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TREATMENT OF PNEUMOCOCCAL PNEUMONIA WITH PENICILLIN*

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ALTHOUGH the sulfonamide drugs are highly effective in the treatment of the pneumococcal pneumonias, serious problems sometimes arise in their administration. In patients with underlying cardiac or renal disease there may be considerable difficulty in maintaining proper fluid balance and in preventing urinary-tract complications while the drugs are being given in adequate doses. Some of the toxic effects of the sulfonamides may not only be dangerous in themselves but may make it necessary to discontinue this therapy before the infection is adequately controlled. Moreover, occasional cases apparently fail to respond to treatment with adequate doses, either because the organism is not susceptible or for other reasons.

Penicillin, on the other hand, seems to be free from many of these difficulties and at the same time is extremely effective against the pneumococcus. In-vitro tests have shown that pneumococci are highly susceptible to penicillin.[1–6] This has been confirmed in the treatment of experimental infections in mice[7,8] and in chick embryos.[9] Resistant strains from clinical cases have not been reported, although strains have been made resistant in vitro[10] and by serial passage through mice treated with subeffective doses of the agent.[11] Both sulfonamide-sensitive and sulfonamide-resistant strains seem to be equally susceptible to the action of penicillin.[12,13]

Tillett, Cambier and McCormack[14] report excellent results in the treatment of 46 cases of lobar pneumonia with penicillin. These cases were mostly of pneumococcal etiology and were of average severity. Others[15,16] reporting miscellaneous groups of infections treated with penicillin have included small numbers of cases of pneumococcal pneumonia in which similar results were obtained.

It is the purpose of this paper to report the results of treatment with penicillin in a series of 54 rather severe cases of pneumococcal pneumonia. Penicillin was used alone in 37 of these cases, whereas in the remaining 17 cases it was given only after sulfonamide drugs had either failed to bring about a satisfactory response or produced untoward effects that made it undesirable to continue their use, although the patients were still acutely ill.

MATERIAL AND METHODS

Selection of Cases

All the patients had pneumococcal pneumonia and were admitted to one of the medical services of the Boston City Hospital from March through December, 1944. The 37 patients who were treated with penicillin alone (Group I) had not previously received sulfonamides for this illness. This was determined from the history and confirmed, when there was any doubt, by the failure to find any sulfonamide in the blood taken on admission. All these patients had pneumococci that were readily typed directly from the sputum by the Neufeld method at the time of entry. Sulfonamides or specific antiserums were not used during the penicillin treatment in these cases.

The remaining 17 patients (Group II) had received sulfonamides, usually in full doses, before the penicillin was started, and the change to the latter was made for one or more of the following reasons. In most cases, the clinical condition became worse. In 1 such case the penicillin was begun after fourteen hours on sulfonamides, and in 10 others after more than thirty hours. In 2 cases, peripheral vascular collapse or congestive failure developed. In 7 cases, there was clinical evidence of a spread of the pulmonary lesion after thirty hours or more on sulfonamides. In 5 cases, positive blood cultures were obtained thirty-six hours or more after sulfonamides were started. In 1 case, there was persistence of

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marked toxemia and leukopenia. In 2 cases, the patients were in extremis on entry after receiving undetermined amounts of sulfonamides. In 1 case, there were severe renal complications of sulfonamide therapy. Other factors that influenced the decision to change to penicillin included the advanced age of the patient, elevation of the blood nonprotein nitrogen and severe underlying disease or prolonged sulfonamide therapy without adequate improvement.

Some of the salient features of all the cases are summarized in Table 1. On the whole, they represented severe cases by all the usual criteria. More than two thirds of the patients were over forty years old. Penicillin was started in most cases after the fourth day of the disease. The majority had two or more lobes involved and appeared clinically to be severely ill, with delirium, evidence of peripheral vascular collapse — cold clammy skin, cyanosis and low blood pressure — or congestive failure. More than half the patients had positive blood cultures. The pneumococci were predominantly of the lower or so-called "common" types, but there were 2 cases in each group in which a higher type of pneumococcus was grown from the blood. A few patients had either leukopenia or extremely high white-cell counts before penicillin treatment was started. Several patients had severe underlying diseases, and in 2 cases there were signs of fluid at the time of entry. Judging from these findings, the cases in Group II were somewhat severer than those in Group I.

TABLE 1. *Summary of Data.*

DATA	GROUP I PENICILLIN	GROUP II PENICILLIN AFTER SULFONAMIDE
Total cases	37	17
Male	32	14
Female	5	3
Age of patient:		
Under 40 years	12	5
40-59 years	16	10
60 years and over	9	2
Duration before penicillin:		
Less than 2 days	4	0
2 or 3 days	8	1
4-6 days	14	10
7 days or more	11	5
Unknown	0	1
Number of lobes involved:		
One	16	2
Two or three (unilateral)	12	11
Two or three (bilateral)	9	5
Severity before penicillin:		
Grade 2 (moderately ill)	15	1
Grade 3 (acutely ill and irrational)	9	5
Grade 4 (shock or congestive failure, or both)	13	11
Pneumococcal types:		
Common types (1, 2, 3, 4, 5, 7 and 8)	28	11
Higher types (all others)	9	6
Bacteremia	19	10
Leukocyte count:		
Less than 5000	6	5
5000-10,000	4	1
11,000-30,000	23	10
More than 30,000	4	1
Chronic alcoholism (total cases)*	10	7
With delirium tremens	4	2
With cirrhosis of liver	2	
Deaths	7	3

*Other complicating conditions. — Group I: bronchiectasis, 2 cases; sickle-cell anemia, 1 case; aplastic anemia, 1 case; empyema on admission, 2 cases. Group II: bronchiectasis, 1 case; moderately advanced pulmonary tuberculosis, 1 case; chronic pyelonephritis, 2 cases; arteriosclerotic heart disease, 4 cases (1 with angina and 1 with asthma).

Methods

At the time of admission, sputum was obtained for typing by the Neufeld technic and venous blood was obtained for cultures in broth and agar and, in many cases, for sulfonamide determinations. Some of the sputum was also cultured and the pneumococcus strains were isolated. Additional blood cultures were made at irregular intervals after penicillin was started. In the Group II cases, a culture and sulfonamide determination of the blood were made before the first dose of penicillin. Para-aminobenzoic acid was added to all mediums used for cultures in cases under sulfonamide therapy, and penicillinase* was added in most of the cultures made during penicillin treatment.

In most cases, the pneumococcus strains isolated from the sputum or blood were tested for sensitivity to penicillin by the method of Rammelkamp and Maxon.[17] Concentrations of penicillin in the blood were determined by the method of Rammelkamp.[18]

Penicillin Administration and Dosage

On the whole, the dosage was individualized with respect to the amount and frequency of the injections and the total duration of treatment. The severity of the disease, the clinical response and the concentrations obtained in the blood were all taken into account. Difficulties were encountered in properly maintaining the constant intravenous injections, particularly in the types of case in which that method seemed most indicated. Intermittent intramuscular administration was the most feasible method and was therefore generally used.

Most of the patients classified as Grade 2 or 3 in severity were given from two to six injections of 15,000 units every two hours, and the same amount was given every three hours until there was definite clinical improvement and the temperature had remained below 100°F. for twelve hours. Additional doses of 10,000 units each were then given every three hours for another two or three days. In the severest cases (Grade 4), the same general scheme of dosage was used except that a single dose of 5000 or 10,000 units was given intravenously in some cases at the time of the first intramuscular injection and from six to twelve injections of 15,000 units were given at two-hour intervals, depending on the response of the patient during that time. In most patients with congestive failure or in those with a low urinary output from this or other causes, bacteriostatic levels were usually maintained for somewhat longer periods than in other patients after similar doses. In such cases the interval between doses could therefore be increased.

The average total dose and duration of treatment in each of the various groups of recovered cases are shown in Table 2. The dosages are considerably larger than those used by Tillett et al.[14] but they

*Kindly supplied by Drs. H. J. White and R. O. Roblin, Jr., of the Stamford Laboratories, Stamford, Connecticut.

were not deemed excessive in view of the severity of these cases and the clinical response observed. In the present series, the average dose and duration

TABLE 2. *Average Total Dosage of Penicillin and Duration of Treatment in Recovered Cases.*

TYPE OF CASE	AVERAGE TOTAL DOSAGE OF PENICILLIN	AVERAGE DURATION OF TREATMENT
	units	*hr.*
Group I	411,000	86
Group II	728,000	162
Severity:		
Grade 2	317,000	66
Grade 3	477,000	107
Grade 4	735,000	148
All cases	507,000	107

of treatment were directly proportional to the severity of the disease.

Other Therapy

Supportive and symptomatic therapy, including proper hydration, the use of oxygen, digitalis, sedation and stimulants, was used as indicated. Inadequate attention to some of these details may have contributed to the failures in single cases. The need for a large fluid intake, which is so essential in sulfonamide-treated cases to avoid renal complications, was obviated with the use of penicillin. This was particularly helpful in some of the patients with congestive failure.

RESULTS

Effect on the Clinical Course

The effect on the clinical course may be judged from the duration of fever and of acute symptoms, such as delirium, prostration and dyspnea, after the penicillin was started. These results are summarized in Table 3. About half the patients were

TABLE 3. *Duration of Fever and Acute Symptoms after First Dose of Penicillin in Recovered Cases.*

DATA	GROUP I CASES	GROUP II CASES	ALL CASES
Duration of fever (100°F. or higher):			
12 hours or less	9	4*	13
13–24 hours	5	2	7
25–36 hours	7	1	8
37–48 hours	3	1	4
More than 48 hours	6†	6	12
Duration of acute symptoms:			
12 hours or less	7	0	7
13–24 hours	14	5	19
25–36 hours	5	1	6
37–48 hours	1	3	4
More than 48 hours	3	5	8

*Two of these patients were still acutely ill but had no fever when penicillin was started.

†One of these patients (Case 33) did not become afebrile until after penicillin was stopped and a sulfonamide drug was given.

essentially afebrile and markedly improved symptomatically within twenty-four hours, and most of the remaining ones who had not previously been treated with sulfonamides were essentially recovered by the end of the second day. In 10 cases, the fever continued for one to four days after marked clinical improvement had occurred. In 4 of the Group II cases, on the other hand, symptoms persisted for one to four days after the fever had subsided. In several cases, the persistence of fever and symptoms was associated with active delirium tremens or with the presence of complications. Examples of the clinical course in a few cases are illustrated in Figures 1-7, which show various types of response to penicillin.

Effect on Bacteremia

The results of blood cultures taken in 18 of the bacteremic cases before treatment and again within the first twenty-four hours after penicillin was started are shown in Table 4. In only 4 cases was a positive blood culture obtained after the penicillin treatment was begun, and in each case only a single dose of 15,000 units had been given two or three hours before the positive culture was obtained. In one of these patients (Case 39), the culture taken after the last dose of sulfonamide and before the first dose of penicillin showed no growth. In all 4 of these cases, the blood culture taken six to twenty hours later was negative. In the remaining 14 cases, all the blood cultures taken after penicillin was started showed no growth. These negative cultures were obtained as early as fifteen minutes after the initial dose of penicillin in 1 case, thirty minutes after the first dose in a second case, and two to four hours after treatment was started in five others.

In the 11 bacteremic cases that are not listed in this table, either the patient died before a second blood culture could be obtained or subsequent cultures were negative but were taken after the patient was already afebrile.

Complications

It is noteworthy that no purulent complications developed in either group of cases after penicillin treatment was started. There were 2 cases, however, in which empyema was already present before the penicillin was given. One of these patients died two hours after the first dose. The other also had an early purulent arthritis. He was given five intrapleural injections of 10,000 units each, but it was necessary to resort to surgical drainage for cure. The arthritis in this case responded to a single intra-articular injection of 10,000 units of penicillin. In 1 other patient (Case 51), a Type 4 pneumococcus was obtained from both sputum and ascitic fluid at the time of entry. This patient died with congestive failure after two days on penicillin.

Sterile pleural effusions developed in 2 cases of Group I. Partial atelectasis of the resolving lung occurred in 3 cases of Group I and in 2 of Group II. These complications were associated with persistence of a low-grade fever after the acute symptoms subsided.

Relapse of the pneumonia with the same type of pneumococcus but with involvement of another

lobe occurred in Case 3 (Fig. 1). This patient received only 100,000 units of penicillin in ten hours by constant intravenous injection, and the relapse occurred ten days later. A relapse with a pneumococcus of a different type occurred in Case 46. This patient was a seventy-one-year-old woman who was first treated for Type 3 pneumococcus pneumonia of the right upper lobe that had failed to respond to sulfadiazine. She improved rapidly after penicillin was started, and she had received a total of 370,000 units. Three days after this course was completed she again developed fever, respiratory symptoms, leukocytosis and signs of a diffuse bronchopneumonia and a Type 24 pneumococcus was obtained from the sputum. She responded with complete recovery to a second course of 660,000 units of penicillin. A third patient (Case 20), with underlying pyelonephritis, hypertensive heart disease and persistent azotemia, was successfully treated for a Type 18 pneumococcus pneumonia of the left lower lobe and again one month later for a Type 3 pneumococcus pneumonia of the right lower lobe. The pneumococcus was obtained each time from blood and sputum.

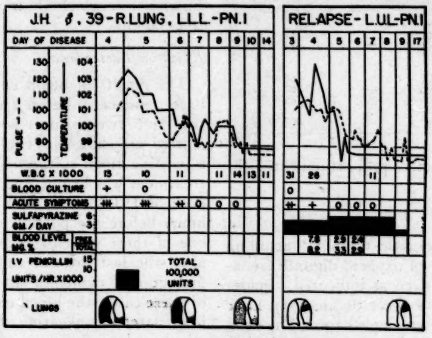

FIGURE 1. *Course and Treatment in Case 3.*

In this case the administration of 100,000 units of penicillin by constant intravenous drip over a period of ten hours was followed by slow but steady improvement. The onset of symptoms of relapse occurred on the third day after the patient was discharged. Type I pneumococci were found in large numbers in the sputum during both attacks.

TABLE 4. *Effect of Penicillin Therapy on Bacteremia.*

Case No.*	Type of Pneumococcus	Blood Culture before Penicillin Treatment: Time after Sulfonamide Begun	Broth	Blood-agar plate	First Blood Culture after Penicillin Begun: Time after first dose	Dosage of Penicillin	Time after last dose	Broth	Blood-agar plate	Second Blood Culture after Penicillin Begun: Time after first dose	Dosage of Penicillin	Time after last dose	Broth	Blood-agar plate
		hr.		*col./cc.*	*hr.*	*units*	*hr.*		*col./cc.*	*hr.*	*units*	*hr.*		*col./cc.*
1	1		+	0	2½	30,000	½	0	0	4½	45,000	½	0	0
2	1		+	12	9	60,000	2	0	0					
3	1		+	0	13½	100,000†	3½	0	0	61½	100,000	51½	0	0
40	1	? 144	+	32	2	15,000	2	+	0	13	75,000	1	0	0
5	2		+	16	8	30,000	2	0	0	54	195,000	3	0	0
17	3		+	0	3	15,000	3	0	0					
27	3		+	33	¼	20,000	¼	0	0	10½	125,000	3	0	0
49	3	72	0	1	2	25,000	2	0	0					
8	5		+	480	2	15,000	2	+	—	8	60,000	2	0	0
38	5	144	+	0	2	20,000	2	0	0	17	120,000	1	0	0
43	7	51	+	32	4	12,500	†	0	0	13	80,000	†	0	0
11	7		+	31	3	15,000	3	+	11	12	60,000	3	0	0
18	7		+	416	¼	20,000	¼	0	0	½	20,000	½	0	0
26	7		+	—	12	75,000	2½	0	0					
54	7	36	+	2	22	160,000	2	0	—					
33	8		+	500	22	160,000	1	0	0	47	310,000	2	0	0
25	19		+	0	17	105,000	2	0	0					
39	25	38	0	0	2	15,000	2	+	0	22	120,000	2½	0	0

*Cases 1-37 received no sulfonamide (Group I); Cases 38-54 received sulfonamide before penicillin (Group II).
†Continuous intravenous administration.

Thrombophlebitis occurred in 2 cases. In neither of them was penicillin given by the intravenous route. In one of these patients the thrombophlebitis developed on the seventh day after a good clinical

response, but later the patient suddenly died following a femoral-vein ligation. In the other patient, sulfonamides had been used first; a posterior tibial thrombophlebitis developed four days after penicillin was started and subsided after six days.

One patient in Group I developed acute cardiac failure and pulmonary edema and died shortly after treatment was started. Auricular fibrillation occurred in 2 of the Group II cases. In one of them, it commenced twelve hours after penicillin therapy was begun and lasted for twenty-four hours; in the other, it began after twenty-four hours of penicillin therapy and lasted for four days. In both cases, restoration of normal sinus rhythm accompanied course of 2,000,000 units given over a period of eleven days.

In Case 43, penicillin was started because of the development of anuria and uremia on sulfadiazine. A drug rash developed six days after the sulfonamide was discontinued and the penicillin was started. The blood-sulfadiazine level at that time was 10 mg. per 100 cubic centimeters, 4 mg. of which was in the free form.

Untoward Effects of Penicillin

Except for a mild burning sensation experienced by several patients at the site of some of the intramuscular injections, there were only two complications that could be attributed to the penicillin. In one case, a left-sided sciatic neuritis developed one week after penicillin treatment was completed. This may possibly have resulted from local nerve injury or from fibrosis about the nerve at the site of penicillin injections. In a second case, a morbilliform rash appeared about the knees, elbows and ankles after 475,000 units of penicillin had been given. The rash persisted for thirty-six hours after all therapy other than penicillin was discontinued, but it could not subsequently be reproduced with a total of 90,000 units given over twelve hours.

TABLE 5. *Relevant Data in Fatal Cases.*

Case No.	Age	Type of Pneumococcus	Duration before Treatment	Initial Blood Culture	Lobes Involved*	Grade of Severity	Penicillin Therapy: Total No. of Injections	Penicillin Therapy: Total Dosage	Penicillin Therapy: Time from First Dose to Death	Comments
	yr.		days					units	hr.	
16	57	1	7	0	Lu,Rl(m)	4	5	75,000	8	Chronic alcoholism; peripheral vascular collapse.
17	59	3	? 8	+	Ruml	4	2	30,000	3	Chronic alcoholism; hypertensive heart disease; congestive failure.
18	36	7	? 4	+	Lul	4	3	60,000	4	Delirium tremens; peripheral vascular collapse.
22	51	1	5	+	Lul	4	1	25,000	1	Peripheral vascular collapse; congestive failure.
23	49	7	7	+	Ruml	4	2	40,000	2½	Empyema; peripheral vascular collapse; congestive failure.
27	61	3†	4	+	Ruml	3	130	410,000	106	Thrombophlebitis (10th day); patient died in shock after femoral ligation; lung abscesses (autopsy).
29	76	4	21	+	Lul	4	1	25,000	½	Arteriosclerotic heart disease with failure; peripheral vascular collapse.
43	56	7	6	+	Ll,Rul	4	‡	300,000	48	Chronic nephritis; anuria(after sulfonamides); patient died in uremia 14 days after penicillin started; lungs clear for 6 days before death.
44	43	3	4	+	Rml	4	2	25,000	2	Chronic alcoholism; bronchiectasis; severe peripheral vascular collapse.
51	54	4	?	—	B	4	18	255,000	46	Chronic alcoholism; cirrhosis of liver; ascites; congestive failure; Type 4 pneumococcus in ascitic fluid.

*R = right; L = left; u = upper; m = middle; l = lower; B = bilateral bronchopneumonia.
†Also had Type B Friedländer's bacillus in sputum and in lung abscesses (autopsy).
‡Continuous intravenous infusion.

improvement in the acute symptoms of the pneumonia.

Active delirium tremens developed in four cases; in each case during the second day of penicillin treatment. In one of the cases of Group I it lasted for four days, and in another it lasted for seven days. In the latter, improvement did not occur until after penicillin was stopped and a sulfonamide was given (Case 33). In one of the Group II cases the active delirium continued for two days; in the other it lasted for three days.

One patient developed hemolytic *Staphylococcus aureus* tonsillitis eight days after penicillin treatment was stopped. Another patient, who had first been treated with sulfonamides, developed an exacerbation of a chronic pyelonephritis with a positive blood culture for hemolytic *Staph. aureus* on the fourteenth hospital day, five days after penicillin treatment was stopped. He recovered after a second

Fatal Cases

Some of the significant findings in the 10 fatal cases are listed in Table 5. For the most part these cases were of extreme severity in patients who were either old or had severe underlying diseases. Almost all of them had multiple-lobe involvement and

bacteremia, and treatment was started late in the disease.

Two of the patients died several days after their pulmonary lesions had apparently cleared. One of them (Case 27) had been treated with penicillin alone and died suddenly after ligation of the femoral vein for thrombophlebitis. Multiple abscesses were found in the lungs at autopsy, and cultures yielded a Friedländer's bacillus. The other patient (Case 43) died of sulfadiazine anuria and uremia after two days of penicillin treatment. A third patient (Case 51) had cirrhosis of the liver, congestive cardiac failure and a Type 4 pneumococcus peritonitis (infected ascites) and died after two days on penicillin. Of the 7 remaining patients, 6 died within four hours of the first dose and one died eight hours after it. These 7 patients were all essentially moribund when penicillin treatment was started.

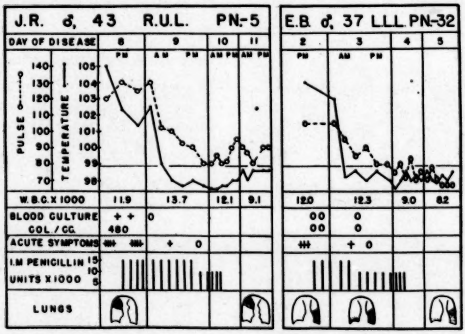

FIGURE 2. *Course and Treatment in Case 8 (left) and Case 15 (right). These charts illustrate the rapid response to penicillin in cases of moderate severity.*

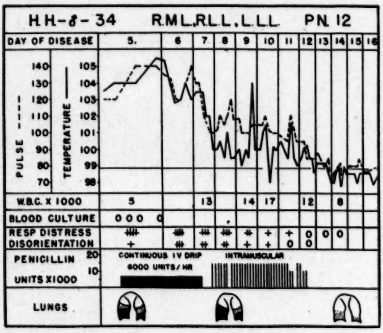

FIGURE 3. *Course and Treatment in Case 12. The chart shows the delayed clinical response to penicillin in a patient who was severely ill but had negative blood cultures.*

Penicillin Sensitivity of the Pneumococcus Strains

Tests for sensitivity to penicillin were carried out on thirty-six strains of pneumococci isolated from as many cases. The results are summarized in Table 6. The minimum inhibiting concentration was 0.016 units or less per cubic centimeter for twenty-seven of the strains, and 0.032 units for the remaining nine strains. In several cases pneumococci of the same type isolated from the blood and sputum of the same patient were tested simultaneously and identical results were obtained with each. Blood levels corresponding to the minimum inhibiting concentrations or higher were rarely maintained for more than two hours after an intramuscular injection of 15,000 units. There seemed to be no correlation, however, between the sensitivity of the strains and the clinical response.

TABLE 6. *Penicillin Sensitivity of Pneumococcus Strains.*

Minimum Inhibiting Concentration	No. of Strains		
	Group I Cases	Group II Cases	All Cases
units/cc.			
0.004	1	—	1
0.008	3	1	4
0.016	18	4	22
0.032	6	3	9
Totals	28	8	36

COMMENT

The results obtained in this series of extremely severe cases of pneumococcal pneumonia indicate that penicillin is a highly effective therapeutic agent in this disease. The results in the Group II cases show, in addition, that penicillin is equally effective in cases that are relatively resistant to

sulfonamide drugs as judged from the clinical and bacteriologic response. Among the 17 cases of this group, 10 had positive blood cultures after treatment with sulfonamides for varying periods up to six days. Only 3 of these patients died after penicillin therapy, one within four hours and the other within two from causes other than the pulmonary infection.

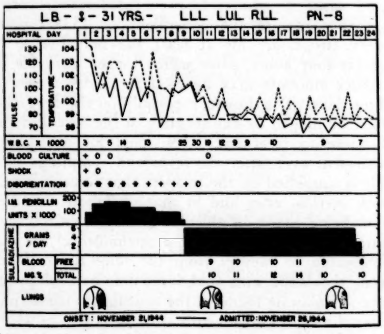

FIGURE 4. *Course and Treatment in Case 33.*

The patient had active delirium tremens and persistent fever and respiratory symptoms during almost eight days of penicillin therapy. She improved rapidly after the penicillin was discontinued and a sulfonamide given. The physical and x-ray findings suggested the presence of interlobar pleural fluid and possibly cavitation in the lung, but the lungs cleared completely without special treatment.

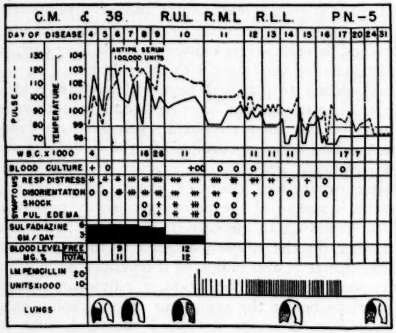

FIGURE 5. *Course and Treatment in Case 38.*

In this patient the symptoms persisted, the pneumonia extended and bacteremia recurred after six days of treatment with sulfadiazine and three days after specific antiserum was given. The bacteremia cleared rapidly but symptomatic improvement occurred slowly after penicillin was given.

There were 10 deaths in this series, a mortality of 19 per cent. Both the Group I and the Group II cases had the same mortality. Among the 46 cases reported by Tillett, Cambier and McCormack[14] there were only 3 deaths (6 per cent). The difference is readily accounted for by the much greater severity of the present cases. Many patients were essentially moribund when treatment was started; seven of them died a half to eight hours after the first dose, and the others had severe complications.

The clinical response to penicillin in the patients who recovered was quite similar to that which occurs under sulfonamide therapy. Fever and acute symptoms subside rapidly, usually within twenty-four to forty-eight hours. In general, the severe cases in which there is bacteremia and multiple-lobe involvement and those with various complications respond more slowly than do the milder and uncomplicated cases. Improvement in the general condition as well as in the subjective symptoms often preceded the drop in temperature, as is the case with sulfonamide therapy. The definite impression was gained that in the extremely severe cases this objective and symptomatic improvement was prompter with penicillin than in similar cases treated with sulfonamides. This may be related to the lag phase in the action of sulfonamides, which probably occurs in patients as well as in the test tube. Delays in the clinical response under penicillin therapy have usually been associated with other underlying diseases, with mixed infections or with purulent or other complications. In severe but otherwise uncomplicated cases a delay in response may result from inadequate dosage.

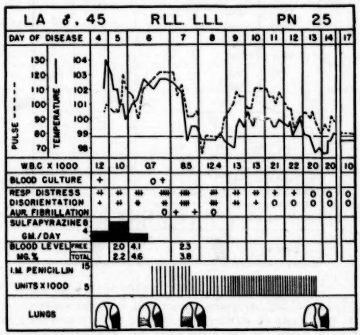

FIGURE 6. *Course and Treatment in Case 39.*

There was a recurrence of bacteremia, together with persistence of a marked leukopenia and extension of the pneumonia, after two days of sulfonamide therapy. A slow but steady improvement occurred under treatment with penicillin.

Penicillin obviously has a distinct advantage over sulfonamides in patients with cardiac, renal or hepatic disease, in whom there is often difficulty in maintaining a proper fluid balance. With peni-

cillin it is not necessary to give alkalies and large amounts of fluids, which may result in serious water retention in such cases. Moreover, there is some evidence that in patients having a relatively low urinary output, and particularly in those with azotemia, higher penicillin levels are more readily maintained than in those with normal cardiorenal function having a large fluid output.

The failure of purulent complications to develop after penicillin treatment was begun is of interest in view of the severity of these cases and the high incidence of bacteremia. This is probably related to the effect that penicillin has in reducing the invasiveness of the susceptible organisms, as indicated by the prompt clearing of the bacteremia

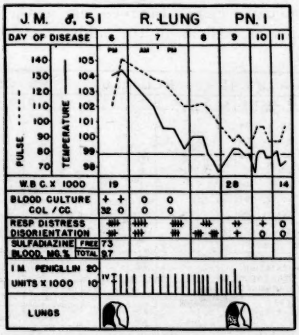

FIGURE 7. *Course and Treatment in Case 40. This patient had a severe pneumonia with involvement of the entire right lung on admission. He had been treated with sulfadiazine at home for about six days and had an adequate blood level of the drug on entry to the hospital. There was a steady drop in temperature after penicillin treatment was started, and clinical improvement followed.*

after penicillin was started. On the other hand, the failure of some established purulent complications to clear following parenteral penicillin therapy is probably due to the failure of the agent to penetrate the infected foci in adequate amounts. It is possible, however, that early and more intensive treatment might result in the clearing of some of these focal infections before they become well established, as is often the case with sulfonamide therapy. Local instillation of penicillin into purulent foci may bring about additional cures. It should be emphasized that early diagnosis and treatment are still extremely essential if success is to be attained in saving life and in preventing serious complications.

It is not possible, on the basis of the available data, to define the effective dosage of penicillin for cases of pneumonia. The amounts used in the present cases were considerably greater than those employed by Tillett. These results suggest that the larger amounts were probably necessary and were not excessive in view of the greater severity of the cases. Whereas as little as 10,000 units given intramuscularly every three or four hours for twenty-four to forty-eight hours may be adequate for some mild cases in adults, cases of moderate severity probably require the equivalent of 15,000 units every two hours for at least the first twelve to twenty-four hours, after which longer intervals or smaller amounts may be used for another two or three days. The dosage, especially on the first day, must be judged by the severity of the case and the response to treatment. The need for continuing treatment even after the fever and symptoms subside is suggested by the relapses that have occurred both in this series and in that of Tillett. Studies now being made in this laboratory indicate that during penicillin therapy the pneumococci are not eliminated so rapidly from the lung as they are from the blood and that large numbers of pneumococci may be found in the sputum for some time after clinical improvement has occurred.

It is still too soon to define the exact place of penicillin and sulfonamides in the treatment of pneumococcal pneumonias. On the basis of the present experience, taking into account the established effectiveness of both agents and the temporary limitation of supply of penicillin, the indications for penicillin may be stated tentatively as follows.

Penicillin is the treatment of choice and should be used from the start in the following cases: in patients who are extremely ill and in a shocklike state; in patients with severe cardiac, renal or hepatic damage, particularly if there is edema or azotemia; if there is severe leukopenia; and in patients who are known to be sensitive to sulfonamides and have rashes, fever or severe nausea and vomiting early in the course of treatment with these drugs.

A change to penicillin from sulfonamides is indicated in patients who have received adequate doses and attained adequate blood levels but have failed to respond with improvement in the symptoms and a significant drop in temperature and pulse rate after twenty-four hours or longer, particularly if there is spread of the pulmonary lesion, persistent bacteremia or an increase in the number of pneumococci in the sputum as seen in direct smears; this change is also indicated if leukopenia, delirium tremens, auricular fibrillation or pulmonary edema develops before the symptoms of pneumonia have cleared or if severe untoward reactions, such as acute hemolytic anemia, gross hematuria, oliguria, anuria, nitrogen retention and even drug rash, occur before the pulmonary infection has been controlled. Crystalluria or microscopic hematuria need not be considered a cause for stopping sulfonamides but is an indication for alkalies and for increasing the fluid intake. Penicillin may be used locally when infected pleural fluid or other accessible foci of infection develop, and oral sulfonamides may be continued in such cases.

Summary and Conclusions

Penicillin was used in the treatment of 54 severe cases of typed pneumococcal pneumonia. Sulfonamides had previously failed to control the infection in 17 of these cases.

Bacteremia cleared rapidly, usually after the first dose of penicillin. Fever and acute symptoms subsided in most cases within twenty-four to forty-eight hours. Subjective improvement often preceded the drop in temperature.

There were 10 deaths. Seven of these were in moribund patients and occurred within a few hours after treatment was begun; the other 3 were associated with severe complicating conditions.

Purulent complications did not develop in any of these cases following penicillin therapy.

Penicillin was equally effective in the patients in whom it was used alone and in those who had previously failed to respond to sulfonamides.

Tentative indications for penicillin are given, and the dosage is discussed.

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LISTERELLOSIS

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LISTERELLOSIS is a sporadic, infectious disease occurring naturally in man[1–22] and in animals,[23] including cattle, sheep, goats, swine, foxes, chickens, rabbits, guinea pigs, gerbils and rats.[24] The disease is caused by *Listerella monocytogenes* (Bergey) and is characterized by symptoms principally referable to the central nervous system.

The causative organism, *List. monocytogenes*, was first submitted as a new species (*Bacterium monocytogenes*) in 1924 by Murray, Webb and Swann,[25] who isolated it from an epizootic affecting their laboratory rabbits and guinea pigs. In 1929, Nyfeldt[21] recovered the organism from the blood stream of a seventeen-year-old boy[6] with infectious mononucleosis, thereby being the first observer to prove definitely that *List. monocytogenes* is harbored by human beings. In 1918, Dumont and Cotoni[2] studied a diphtheroid organism isolated from the cerebrospinal fluid of a twenty-four-year-old soldier, which Paterson[26] over twenty years later identified as *List. monocytogenes*. It is highly probable that the diphtheroid organisms isolated from cases of meningitis in 1915 by Atkinson[1] and in 1919 by Dick[3] were Listerella.

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Epidemiology

Far too few cases are available for study to yield any clear-cut epidemiologic pattern of human listerellosis. Sufficient information is known, however, to avoid some blind pathways of exploration in an attempt to construct an epidemiologic fabric.

Including the probable cases,[1, 3–5, 10] — that is those in which the isolated organisms were described as diphtheroids but appear to have been Listerella, — listerellosis in human beings has been reported in Australia, France, Denmark, Scotland, Norway, Uruguay, Argentina, England and the United States (Illinois, Iowa, New York, Connecticut, Massachusetts, North Carolina, Missouri and California) (Table 1). Areas other than those cited for human infection in which spontaneous listerellosis has been recognized in animals include Sweden, South Africa, New Zealand, Germany and Russia, as well as Indiana, New Jersey, Colorado, Oregon, Minnesota, Arkansas, Vermont and Virginia.[23] Thus, it is quite evident that *List. monocytogenes* is well dispersed throughout the world.

A noteworthy fact is that Paterson's study of fifty-four strains of Listerella[26] revealed no relation between the bacteriologic type and the zoologic host species (man and animals), nor did the types

TABLE 1. *Data of 36 Human Cases of Listerellosis.*

AUTHOR	DATE OF OCCURRENCE	STATE OR COUNTRY	AGE	SEX	CLINICAL DIAGNOSIS	BLOOD CULTURE	SPINAL-FLUID CULTURE	OUTCOME
Atkinson[1]	1915	Australia	2 yr.	M	Meningitis	Not done	Diphtheroid	Death
			4 yr.	M	Meningitis	Not done	Diphtheroid	Death
			3¾ yr.	F	Meningitis	Not done	Diphtheroid	Death
			9 yr.	F	Meningitis	Not done	Diphtheroid	Death
			2 yr.	M	Meningitis	Not done	Diphtheroid	Recovery
Dumont and Cotoni[2]	1918	France	24 yr.	M	Meningitis	Negative	Diphtheroid (identified as Listerella by Paterson[20])	Death
Dick[3]	1919	Illinois	49 yr.	M	Meningitis	Diphtheroid	Diphtheroid	Death
Baldridge et al.[4*]	About 1925	Iowa	Not given	Not given	Infectious mononucleosis	Diphtheroid	Not done (diphtheroid isolated from lymph-node biopsies)	Recovery
			Not given	Not given	Infectious mononucleosis	Diphtheroid		Recovery
			Not given	Not given	Infectious mononucleosis	Diphtheroid		Recovery
			Not given	Not given	Infectious mononucleosis	Diphtheroid		Recovery
			Not given	Not given	Infectious mononucleosis	Diphtheroid		Recovery
Kessel and Romanoff[5]	1929	New York	39 yr.	M	Meningitis	Diphtheroid	Diphtheroid	Recovery
Nyfeldt[6]	1929 and 1930	Denmark	17 yr.	M	Infectious mononucleosis	Listerella	Not done	Recovery
			33 yr.	M	Infectious mononucleosis	Listerella	Not done	Recovery
			19 yr.	F	Infectious mononucleosis	Listerella	Not done	Recovery
Burn[7]	1933 and 1934	Connecticut	1 day	M	Meningitis	Listerella		Death
			Premature infant	F	Meningitis	Listerella		Death
			8 days	F	Meningitis	Listerella	Listerella	Death
			53 yr.	M	Meningitis		(Type 3 pneumococcus and Listerella isolated from brain)	Death
Schultz et al.[8]	1933	California	Adult	F	Meningitis	Not done	Diphtheroid (identified as Listerella by Webb and Barber[22])	Recovery
Gibson[9]	1934	Scotland	37 yr.	M	Meningitis	Not done	Diphtheroid (identified as Listerella by Webb and Barber[22])	Death
Tesdal[10]	1934	Norway	31 yr.	F	Meningitis	Negative	Diphtheroid	Death
Burn[11]	1935	Connecticut	26 yr.	M	Meningitis	Not done	Not done (Listerella recovered from brain)	Death
Carey[12]	1935	Massachusetts	3¾ yr.	M	Meningitis	Not done	Listerella	Recovery
Poston et al.[13]	1936	North Carolina	3 yr.	M	Meningitis	Not done	Not done (Listerella recovered from brain)	Death
Porzecanski and De Baygorria[14]	1937	Uruguay	19 yr	M	Meningitis	Not done	Listerella	Recovery (patient treated with Prontosil 27)
Schmidt and Nyfeldt[15]	1937	Denmark	16 yr.	F	Infectious mononucleosis	Negative	Listerella	Recovery
			18 yr.	F	Infectious mononucleosis	Negative	Listerella	Recovery
			24 yr.	M	Infectious mononucleosis	Listerella	Listerella	Recovery
			14 yr.	M	Infectious mononucleosis	Listerella	Listerella	Recovery
Wright and MacGregor[16]	1938	Scotland	1½ yr.	M	Meningitis	Not done	Listerella	Death
Porter and Hale[17]	1939	Iowa	Child	M	Meningitis	Not done	Not done (Listerella isolated, but source not given)	Recovery (patient treated with sulfanilamide)
Pons and Julianelle[18]	1939	Missouri	16 yr.	F	Infectious mononucleosis	Listerella	Not done	Recovery
Savino[19]	1939	Argentina	67 yr.	F	Meningitis	Negative	Listerella	Recovery (patient treated with sulfapyridine)
Webb[20]	1943(?)	England	20 yr.	M	Infectious mononucleosis	Listerella	Not done	Recovery

*In Baldridge's cases the diagnosis of listerellosis is doubtful.

appear to be associated with a particular geographic origin.

To date, the number of human cases from which *List. monocytogenes* has been isolated and identified is 23. Adding the probable cases, the total becomes 36. Of these 36 cases, 15 (42 per cent) terminated fatally. Computing the fatality after subtracting 14 cases diagnosed as infectious mononucleosis (for reasons given below), the mortality of human listerellosis in its typical meningeal form approximates 68 per cent. This latter figure would be higher (79 per cent) if the recent cases treated with sulfonamides were excluded.

The natural habitat of the organism is not known. The part played by animals as a reservoir of infection for human beings is questionable. Their role appears to be unimportant, but any opinion on this score should be given reservedly until there accrue more data on human infection. It is noteworthy, however, that in areas in which listerellosis is enzootic (the United States, — Illinois, New York and Iowa, — England, Germany and New Zealand), very few cases of human infection have been reported. Indeed, in only a single case of human infection has there been recorded the remotest possibility of exposure (to a pet rabbit ill with so-called "snuffles" that was not further examined[7]).

Other than probable transplacental infection occurring in the newborn,[7] the portal of entry of the organism in human beings is obscure. Julianelle[27] thinks that ingestion and penetration through the gastrointestinal tract are likely because of the successful infection of white mice by means of contaminated drinking water, whereas inoculation of a culture intranasally into highly susceptible rabbits failed to cause infection. In domestic animals, experimental production of listerellosis to simulate a spontaneous infection is difficult regardless of the method of infection utilized. The nasal route appears to be the likeliest pathway in natural infection of animals[28, 29] but further work is needed to resolve this question.

Except for a convalescent carrier,[8] the isolation of *List. monocytogenes* has been accomplished only in actively diseased animals and man. The few attempts to discover healthy carriers in man have met with failure.[7] These few negative findings by no means eliminate the possibility of latent, indiscernible infection that flares into active disease under propitious conditions. The latter explanation, for example, can be applied to those cases of infection of the newborn that have occurred in human beings,[7] cows[30, 31] and sheep,[32] in which the parent was apparently unaffected by the organism. Predisposing causes that are capable of producing a general lowering of resistance have been reported in several human cases,[1, 3, 5, 7, 13, 16] and these are believed to exert an appreciable influence in producing the disease in animals.

All age groups and both sexes have been affected with listerellosis. The occurrence of the disease in the newborn,[7] one of these patients being a three-week premature infant, is particularly interesting because of the incrimination of Listerella as a cause of abortion in cattle[30–33] and sheep.[32]

The isolation of *List. monocytogenes* from the blood or cerebrospinal fluid in 9 cases of infectious mononucleosis (Table 1) merits separate consideration. Three other isolated strains mentioned by Paterson[26] are not considered in this paper because of insufficient data. Murray, Webb and Swann[25] first noted the typical mononuclear response in the blood of rabbits affected with listerellosis. It was to be expected, therefore, that the blood picture seen in human beings with infectious mononucleosis would be ascribed to the same cause.[6, 15] The available evidence, however, controverts this assumption. A filterable virus associated with infectious mononucleosis has been shown by van den Berghe, Liessens and Kovacs[34, 35] and Nettleship.[36] Julianelle, Bierbaum and Moore[37] were unable to confirm these findings. Paterson[26] studied the antigenic structure of fifty-four strains of Listerella isolated from a variety of animals and from human beings. Ten of these strains were isolated from patients with infectious mononucleosis, and they comprised a distinct group (Group 3) in his classification of four groups. Serologic evidence against an etiologic relation between Listerella and infectious mononucleosis has been demonstrated by Kolmer,[38] Julianelle[27] and Janeway and Dammin.[39] Furthermore, the benignity of the cases of infectious mononucleosis from which *List. monocytogenes* was isolated, in contrast to the high mortality that occurred in the typical meningeal form of listerellosis, supports the likelihood that the organism was acting in the capacity of an adventitious invader. The possibility of a mutual relation between the discovered filterable virus and *List. monocytogenes* in the pathogenesis of infectious mononucleosis should be kept in mind. In this respect, the well-known virus-bacteria combination in the production of swine influenza may be pointed out as an established fact.

The sporadicity of human listerellosis indicates a low degree of communicability. A study of the case histories, however, reveals some possibly significant facts. Burn[7] reported 2 infants born the same day in the visiting obstetric service of a hospital. The infant delivered early in the morning died the next day of listerellosis. The second infant, apparently delivered later on the same day, suddenly became ill eight days later and died of listerellosis within six days. Atkinson's[1] 5 cases in children all occurred within a period of thirteen days. Until further information is available concerning interhuman communicability of listerellosis, it is unwise to ascribe the cited cases to pure coincidence.

Thus, the usual communicable-disease precautions should be applied to listerellosis. There is little question of the communicability of the disease in animals.

Symptoms and Signs

Because of the protean symptomatology of infectious mononucleosis and the likelihood that a Listerella is merely a fortuitous invader in the disease, only the meningeal form of listerellosis will be considered.

The usual clinical picture seen in all ages is that of a septicemia with severe meningoencephalitic involvement. In children and adults the following observations have been made: sudden or gradual illness with fever, vomiting, headache, lethargy, stupor, irrationality, loss of reflexes, convulsions, rigidity of the neck, strabismus, ptosis, diplopia and bilateral mastoiditis. In fatal cases, death usually occurred within a week. Many patients who recovered had a prolonged convalescent period. In 1 case, affecting a nurse,[8, 22] ten weeks after the inception of symptoms a speech defect, impaired memory, emotional instability, difficulty in self-feeding, slight nodding of the head and a sprawling gait were present. *List. monocytogenes* was recoverable in the cerebrospinal fluid for over four months. In the newborn, signs were apparent at birth or two to eight days later.[7] Refusal of food, diarrhea, cyanosis, drowsiness and clonic convulsions were noted. The 3 cases reported ended fatally within six days.

Laboratory Findings

The cerebrospinal fluid has shown the most consistent changes. Increased pressure, a positive Pandy reaction, an increased number of leukocytes (predominantly lymphocytes), intracellular and extracellular Listerella organisms in stained smears and recovery of the organism in pure culture have been recorded.[1–3, 5, 8, 10, 12, 13, 16, 18, 19]

A moderate leukocytosis has been the one common hematologic observation in the few blood examinations performed. The interpretation of the differential count has been confused because of changes attributable to infectious mononucleosis when the latter disease has accompanied the isolation of *List. monocytogenes* from the blood. In cases in which listerellosis alone was present, neutrocytosis was originally found.[7, 9, 12–14, 19]

Post-Mortem Findings

The post-mortem findings included suppurative leptomeningitis and ependymitis, purulent otitis media, focal necrosis and patchy fatty degeneration of the liver, a swollen and congested spleen, focal necrosis of the adrenal glands, atelectasis, focal pneumonia and bronchiolitis.[1, 7, 9, 13]

Treatment

Before the advent of the sulfonamides, symptomatic treatment had been relied on with little success. Three patients with the meningeal form of listerellosis were treated with sulfanilamide,[17] sulfapyridine[19] and Prontosil, respectively.[40] Recovery ensued in all 3 cases.

Experimentally, Webb[20] achieved favorable results with sulfanilamide and sulfapyridine in mouse listerellosis. His best results were obtained with a therapeutic combination of sulfapyridine and specific antilisterella rabbit serum. Savino[41] infected white rats with *List. monocytogenes* and noted a protective action with sulfapyridine. Porter and Hale[17] reported that both sulfanilamide and sulfapyridine were therapeutically effective in mice experimentally infected with listerellosis. In-vitro tests showed penicillin to be ineffective against *List. monocytogenes*.[42]

Summary

There have been reported in the literature 23 definitely diagnosed and 13 probable cases of human listerellosis. In its typical meningeal form, this disease showed a mortality of approximately 79 per cent, excluding 3 cases treated with sulfonamides.

Ecologic, age and sex factors appear to be of little significance in the incidence of this disease.

The natural habitat and portal of entry of *Listerella monocytogenes* — other than transplacental infection in the newborn — are unknown. The nasal and gastrointestinal tracts appear as the likeliest routes of penetration.

The status of a healthy or latent carrier of *List. monocytogenes* has not been proved in man or animals. The facts that infection of the newborn can occur with no effect on the parent, that a Listerella bacteremia may be present in cases of infectious mononucleosis and that certain predisposing factors apparently produce active infection, however, suggest that latent carriers play a significant role in the pathogenesis of listerellosis.

At present there is little evidence to incriminate animals as direct transmitting agents of *List. monocytogenes* to human beings. The widespread prevalence of listerellosis in animals, however, establishes them as possible reservoirs of infection for man.

The significance of *List. monocytogenes* in cases of infectious mononucleosis is discussed. It is believed that the organism acts as a contingent invader in infectious mononucleosis rather than as an incitant of the disease. The possibility of a mutual virus-bacteria relation in infectious mononucleosis is pointed out.

Circumstantial evidence is cited supporting the possibility of interhuman communicability in active cases of listerellosis, thus making advisable the practice of communicable-disease precautions whenever this disease is encountered.

Clinically and at autopsy, listerellosis is characterized by a meningoencephalitic syndrome. The most usual spinal-fluid changes were increased pressure, globulin and leukocytes. A moderate neutrocytosis occurred early in the disease.

Treatment with Prontosil, sulfanilamide and sulfapyridine appears to have been successful.

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MEDICAL PROGRESS

SKIN TESTS IN BACTERIAL AND VIRAL DISEASES* (Concluded)

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SKIN TESTS EMPLOYING BACTERIAL TOXINS

Schick Test

In 1908, Schick[85] showed that the toxin of the diphtheria bacillus is capable of eliciting dermal reactions in certain persons. His subsequent publications[86, 87] announced that this test could be used as an index of immunity or susceptibility to diphtheria. His experiments indicated that a negative intracutaneous reaction usually means a high enough level of antitoxin to protect against the disease. The test dose of toxin was originally defined by Schick on an empirical basis as 1/50 of a guinea-pig M. L. D. (minimal lethal dose). This level was selected by him because he thought that persons who failed to react to this dose possessed sufficient antitoxin to protect them against all but the so-called "septic type" of diphtheria. In subsequent years when cases of diphtheria were reported in Schick-negative reactors there was some question whether the Schick test dose of 1/50 M. L. D. should not be increased. This problem was considered in 1931 by the Biological Standardization Commission of the League of Nations, and the 1/50 M. L. D. recommended by Schick was adopted by the commission as representing the optimal test dose. It was further recommended that Schick toxin be standardized by determining its combining power as well as its toxicity. The reason for this recommendation is that filtrates of diphtheria cultures contain varying quantities of substances that although unable to elicit the dermal reaction can combine with antitoxin. Hence, toxin standardized by means of toxicity alone varies in its ability to elicit dermal reactions, depending on the extent to which antibody has been eliminated locally by these nontoxic substances. The validity of these recommendations has been questioned by Taylor and Moloney,[88] who were unable to find that the combining power of Schick toxin had any significance for human beings with respect to the level of antitoxin detected. Furthermore, they recommended a dose of toxin containing three times the level usually employed (1/50 M. L. D.). Thus the question of the proper toxin level to be used in the Schick test is still an open one.

In 1913, Schick[86] noted that occasionally false-positive dermal reactions may occur. These reactions appeared a little earlier than the true reactions, reached their maximum intensity sooner and faded more quickly. Bessau and Schwenke[89] found that, when the toxin is destroyed by heat, false-positive reactions still occur. As a result of this observation, a control injection of heated toxin was introduced into the Schick test. It soon became apparent that this so-called "pseudoreaction" was due to hypersensitivity to the protein of the diphtheria bacillus. The reaction is highly specific and indicates some previous contact with the diphtheria bacillus. It is usually absent in infants and becomes more frequent as age advances. Further experience with the Schick control showed that immunizing injections often gave rise to unpleasant reactions in those exhibiting pseudoreactions. Thus the control not only came to serve as an indicator of false-positive reactions, but also indicated those subjects who might react severely to immunizing injections.

Moloney and Fraser[90] have advised employing a 1/20 dilution of diphtheria toxoid as a substitute for the heated-toxin control in the Schick test. They believe that this material is a better control, as well as an efficient indicator of those persons who will give severe reactions when immunized with toxoid. These reactions usually consist of chills, fever, general malaise, nausea and vomiting. This test has been frequently referred to as the Moloney test. Although it is of unquestioned value in determining when subjects are hypersensitive to bacterial protein, — and hence should be immunized cautiously with toxoid, — it is not a true control because the toxoid may contain one hundred times as much bacterial protein as does the Schick toxin. As a consequence of the higher bacterial protein content more persons react to the Moloney control than to the Schick control, thus making the Schick test more difficult to interpret.

The Moloney test, however, should be done on all Schick-positive subjects over the age of five who are to be immunized with toxoid.[91] The 1:20 dilution of toxoid originally proposed by Moloney and Fraser was found to be too strong, and as a result a dilution of 1/100 is most generally used at present. The test is performed by injecting 0.1 cc. of a 1:100 dilution of toxoid into the volar surface of the forearm. Readings are made in twenty-four and forty-eight hours. Significant reactions consist of an area of erythema greater than 1 cm. in diameter. Bunch and his co-workers[92] have recommended a scheme of immunization that is dependent on the degree of sensitivity to bacterial protein as demonstrated by the Moloney test.

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. The Schick test is performed by injecting 0.1 cc. of Schick toxin intradermally in the volar surface of the right forearm. This is controlled by injecting the same volume of heated toxin in the same manner in the left arm. Readings should be made at the end of two and of four days and are interpreted as follows:

Positive reaction. An area of erythema and infiltration measuring at least 10 mm. in diameter appears in twenty-four to thirty-six hours on the right arm and reaches its greatest intensity in four or five days. There should be no reaction on the left (control) arm. This response indicates susceptibility to diphtheria.

Positive-combined reaction. Reactions measuring at least 10 mm. are present on both arms in two days. The control reaction, however, fades by the fourth day, the time when the true reaction reaches its height. This response indicates susceptibility to diphtheria and sensitivity to diphtheria-bacillus protein.

Pseudoreaction. Reactions occur on both arms and run a similar course, reaching a peak on the second or third day and fading by the fourth. Persons showing this response are hypersensitive to diphtheria-bacillus protein but presumably immune to diphtheria.

Negative reaction. No reaction occurs, or one less than 10 mm. in one or both arms. This indicates that the subject has little or no sensitivity to diphtheria-bacillus protein and is probably immune to diphtheria.

A few reports have appeared in the literature describing cases of acute anaphylactic shock following the application of the Schick test. In 1936, Parish[93] described 14 cases of this character. Two of these patients were known to be sensitive to Witte peptone, an agent added to the toxin in order to stabilize it.

Following the acceptance of the Schick test dose as 1/50 M. L. D., a large number of experiments have indicated that this amount of toxin does not produce a dermal reaction on intracutaneous injection into human beings if the blood serum contains more than 1/30 unit of antitoxin per cubic centimeter. This value had for many years been generally regarded as representing the so-called "Schick level" of immunity. During the last few years, however, a number of reports have appeared indicating that this level is more accurately described by a considerably smaller amount of antitoxin. Glenny and Waddington[94] found that the Schick-negative level in guinea pigs corresponds to 1/250 unit of antitoxin per cubic centimeter of serum. Others[95] have shown that the level in man lies between 1/500 to 1/250 unit per cubic centimeter. Although Phair[96] accepts 1/100 unit of antitoxin as the threshold level, he found that 9.3 per cent cases of the Schick-positive group that he tested had sufficient antitoxin so that the test should have been negative. In addition, 7.5 per cent of the negative reactors had a level of antitoxin that should have rendered them positive. These conflicting results indicate that with the methods for measuring antitoxin now available, there is no precise Schick level of antitoxin that can be determined above which a person will be protected and below which he will be susceptible.

The failure to find a critical level of antitoxin as measured by the Schick test has cast some doubt as to its value as an index of susceptibility or immunity. Obviously only by long-continued observation of the behavior of groups of positive and negative Schick reactors can the value of this test be established. Although there are exceptions, the bulk of evidence that has accumulated since Schick's original publication in 1908 indicates that a negative Schick reaction means resistance against all *ordinary* risks of infection. This evidence is based on the following observations: there is almost no diphtheria in nurses who are Schick negative despite repeated exposures; there is an extremely low incidence of the disease in Schick-negative reactors in the population at large; virulent organisms can exist in the throats of Schick-negative reactors without producing the disease; and the results of challenge experiments add more evidence. Guthrie, Marshall and Moss[97] inoculated Schick-positive and Schick-negative persons with virulent diphtheria organisms and observed the disease in the former only. O'Brien, Okell and Parish[98] had occasion to observe an inadvertent experiment in which ten to twenty presumably lethal doses of toxin for man were injected intradermally into a known Schick-negative reactor; no symptoms occurred.

It must be kept in mind that immunity in diphtheria, as in any infectious disease, is only relative. Not only does the level of immunity fluctuate, but it may be broken down by massive infection. Despite this, the number of cases occurring in Schick-negative reactors is relatively few. O'Brien, Okell and Parish[98] followed 20,000 Schick-negative subjects for six years and were able to trace 18 cases of diphtheria, 17 of which were mild. Neale[99] reported 2 cases in Schick-negative persons, and Bauer[100] reported 21 cases occurring out of a total of 96,252 immunized and Schick-negative persons. Meersseman, Friess and Renard[101] noted a 1 per cent incidence of diphtheria in a Schick-negative group numbering several thousand. Robinson and Marshall[102] have observed 12 cases in which the Schick test was negative immediately prior to the onset of the disease. Underwood[103] reviewed the literature of diphtheria occurring in Schick-negative persons up to 1935 and reported 20 additional cases (1 per cent) occurring in 2761 known Schick negative reactors. In 19 of these cases the so-called "gravis" strain was isolated — an organism that is usually found in the severest cases. This suggests that the Schick test may not be an effective index of immunity against the gravis strain of organism. Many of the above reported cases were severe, showing that the disease is not always mild in Schick-negative cases. Parish and Okell[104] have shown that 1.1 per cent of 533 children who were originally Schick negative relapsed to a positive state within one to seven years, and 5 per cent of 440 vaccinated children relapsed during the same period. Since

several of the reported cases of diphtheria in Schick-negative reactors were not retested at close intervals, it is possible that the subjects had become Schick positive prior to the onset of the disease.

In summary, it may be stated that although there are reported failures, a negative Schick test usually means sufficient degree of immunity to protect against diphtheria. It is well known that there are persons who, having had an adequate primary stimulus but having lost with the lapse of time most of their demonstrable antitoxin, nevertheless react after exposure with the production of antitoxin rapidly enough to protect against the disease. This is seen in a number of persons who become Schick negative after the injection of the minute amount of toxin used in the Schick test. This of course is likeliest to occur in adults who have had repeated subclinical exposures. It is believed at present that a positive Schick test in adults does not necessarily mean susceptibility, whereas it is a much closer index of susceptibility in children.

Dick Test

In 1924, the Dicks[105] injected 0.1 cc. of a 1:1000 solution of beta-hemolytic streptococcus toxic filtrate intradermally into a number of persons and found that those with no past history of scarlet fever gave an inflammatory response more frequently than did those with positive histories. They also found that this filtrate could be neutralized by convalescent scarlet-fever serum. On this basis they suggested that the skin test could be used as an index of immunity or susceptibility to scarlet fever.*[106] They later reported 20,856 subjects who were Dick negative and went through repeated exposures to scarlet fever without contracting the disease.[107] Despite these rather impressive figures, not infrequent reports have appeared in the literature from time to time describing scarlet fever in Dick-negative reactors.[108–111] Since the Dick test measures only antitoxic immunity, a cause of the apparent failure of the Dick test may be that there is more than one antigenic strain of erythrogenic toxin.[112–114] Theoretically, infection with a streptococcus producing an erythrogenic toxin different from that used in the Dick test could produce a rash in Dick-negative reactors. Another possible source of false-negative reactions is the use of toxin of inferior potency because of the difficulty in standardizing the erythrogenic toxin. Despite the reported failures, it is generally believed that the Dick test is reliable enough to be used as an index of immunity to the rash of scarlet fever. There is no convincing evidence that Dick-negative reactors are less susceptible to streptococcal infections than Dick-positive ones.

Schwentker, Janney and Gordon[110] have recently reported their careful study of a scarlet-fever and tonsillitis epidemic in Rumania that was caused by a Type 10 hemolytic streptococcus. They have clearly shown that although a negative Dick test usually indicates immunity to scarlet fever, a positive reaction does not necessarily mean susceptibility. Thus, in the group who became asymptomatic carriers of the type of streptococcus responsible for the then current scarlet-fever epidemic, there were equal numbers of Dick-positive and Dick-negative reactors. It therefore appears that whether the organism survives in the throat does not depend on the level of antitoxin present. Whether illness does develop apparently depends on the presence or absence of antibacterial immunity. The subsequent clinical character of the infection, however, is determined by the level of antitoxic immunity. Thus, Schwentker and his co-workers[110] have found that 90 per cent of their patients with tonsillitis were Dick negative, whereas 32 of the 34 persons who developed scarlet fever had positive reactions.

It is now recognized that the toxic component of the streptococcus is responsible for the enanthem, exanthem and constitutional reactions found in scarlet fever, characterized by vomiting, generalized lymphadenopathy, arthralgia and albuminuria. Although precise information is lacking, there is no incontrovertible evidence that persons with a negative Dick test are less likely than others to develop septic complications following streptococcal infections. To establish this point definitely it would be necessary to observe an epidemic of scarlet fever and tonsillitis caused by the same type of streptococcus. Although this was done by Schwentker and his co-workers,[110] they gave no clinical description of their cases. Stebbins, Ingraham and Reed[115] found that complications following a milk-borne epidemic of streptococcal pharyngitis (and hence presumably caused by the same type) were as frequent in those with a rash as in those without one. Hobson[116] concluded that complications were even more frequent when a rash was absent.

The Dick test should probably always be controlled with heat-inactivated toxin, since pseudoreactions occur as they do with the Schick test. But the Dick-test material dispensed commercially contains no control material, since it is thought that if broth filtrates of high toxin content are used the protein elements will be sufficiently diluted in the final test material to eliminate the false reactions. It is believed that the pseudoreactions are due to streptococcal protein and are unrelated to the toxin. Unlike the true Dick reaction and like the pseudo-Schick reaction, it is more frequent with advancing age and is found oftener in communities where scarlet fever is or has recently been epidemic.

The Dick test is performed by injecting 0.1 cc. of toxin intradermally into the volar surface of the forearm. The reaction is read in twenty-four hours. An area of erythema measuring at least 1 cm. is

*The reverse of this test is the Schultz–Charlton phenomenon, in which the intradermal injection of immune serum blanches the rash of scarlet fever.

considered a positive reaction. The skin-test dose has been established by the Scarlet Fever Committee as representing the least amount of toxin to which all susceptible persons react positively. This has been determined by skin-testing a large number of children of different ages.

Skin Tests Employing Antigens of Viral Origin

Despite the fact that the change in dermal sensitivity following infection was first demonstrated with a virus (vaccinia), it has only been in recent years that skin reactions with antigens of viral origin have been employed. Lymphogranuloma inguinale is the only viral disease in which a skin test is now widely employed as a diagnostic aid. Recently, investigators have shown that a dermal reaction may be elicited in persons convalescent from mumps. This test has proved of great aid in determining susceptibility or immunity to mumps. Beveridge and Burnet[117] and Kane[118] have independently shown that dermal allergy can be elicited in persons convalescent from influenza. Whether this reaction can be used to determine susceptibility has not been established. With improved methods for growing viruses in high titer, there is reason to believe that skin reactions will be employed with increasing frequency in viral diseases.

Frei Test

Frei's[119] introduction of his test in 1925 made possible the exact diagnosis of lymphogranuloma inguinale and demonstrated that a number of conditions previously considered to be unrelated were diverse manifestations of infection with the virus of lymphogranuloma inguinale. As antigen, Frei used heat-inactivated pus obtained from the unruptured buboes of a patient with lymphogranuloma inguinale. Because of the difficulty in obtaining sufficient material and the possibility that other infectious agents are included, as well as the variation in antigen content, the use of pus from human buboes had major limitations that precluded its widespread use.

Following the demonstration that the virus of lymphogranuloma inguinale can be grown on intracerebral inoculation in mice, Wassen[120] introduced the mouse-brain antigen as a substitute for human pus in the performance of the Frei test. Further experience with this material showed that because of the nonspecific reactions obtained, mouse brain was unsuitable for skin testing.[120–122] When Rake and his co-workers[123] grew the virus of lymphogranuloma inguinale in high titer in the yolk sac of the developing chick embryo, the problem of securing a cheap and ready source of virus was solved. Grace and his co-workers[124] showed that this material gave satisfactory and specific dermal reactions in patients infected with the virus of lymphogranuloma inguinale. Further experience has shown the yolk-sac antigen to be reliable and to be superior to mouse brain in eliciting the dermal response in infected persons.[125, 126] There is some evidence, however, that it may give more false-positive reactions and is less sensitive than human pus.[127–129] The former product is now available commercially under the name of Lygranum.

Extensive surveys have shown the Frei test to be positive in a high percentage (90 to 95 per cent) of persons known to have been infected with the virus of lymphogranuloma inguinale.[130–133] In any group of persons picked at random, however, a number with no history or physical signs of the disease react positively to the antigen.[126, 134] This has been explained on the basis of a latent or veiled infection. Although it is true that accidental laboratory infections in those working with the virus have been acquired via the respiratory tract and the skin of the hand,[135] and that such cases may go unrecognized, there is no evidence that this route of infection occurs in the naturally acquired disease. The question therefore arises whether the positive reactions in persons with no history or physical signs of the disease indicate unrecognized infections or are false-positive reactions. Recently attention has been called to the fact that there is a close antigenic relation between the viruses of lymphogranuloma inguinale, psittacosis, meningopneumonitis, trachoma, inclusion blenorrhea, and the atypical pneumonia virus of Eaton.[136–138] Positive Frei reactions have been obtained in cases of atypical pneumonia due to Eaton's virus.[137] Favour[139] observed a positive reaction in 1 of 4 cases of ornithosis that he tested. In this case the question of a previous infection with the virus of lymphogranuloma inguinale was eliminated on the basis of the history and physical examination. Although it is true that the incidence of positive Frei reactions is higher in persons exposed to venereal disease who give no history or physical signs of lymphogranuloma inguinale, to establish definitely the specificity of the Frei test the frequency of the occurrence of positive reactions in persons infected with the above viruses should be determined. Until this is done, there is reason to question some of the positive reactions obtained in persons who have had no history or physical signs of infection with the virus of lymphogranuloma inguinale.

There is a great deal of variation in the literature concerning when the Frei test becomes positive following infection. Reports have varied from one week to six months.[140–143] Wassen[140] experimentally infected a number of volunteers and found that the Frei test became positive as early as the sixth day following the appearance of the lesions. Harrop, Rake and Shaffer[135] noted positive reaction as early as five to nine days following the symptoms in accidental laboratory infections. Reversal of the Frei test has been observed in persons who were intensively treated with chemotherapy early in the disease.

Since a positive Frei test persists for years, possibly for life, a positive reaction does not necessarily mean that a given disease under consideration is due to infection with the virus of lymphogranuloma inguinale. Also, a negative reaction does not necessarily mean that it can be ruled out, since unmistakable cases have been reported with negative reactions to potent antigens.[144] In these cases diagnosis may be established by using the so-called "inverted Frei test." In this test pus from the infected patient injected into persons known to be Frei positive induces a positive dermal reaction.

The Frei test is performed by injecting 0.1 cc. of the antigen intradermally in the forearm. A control injection, consisting of the same volume of uninfected chick-embryo material, is performed in the other arm. A positive reaction consists in the presence of an area of infiltration or a nodule measuring at least 5 or 6 mm. in diameter that is present at the end of forty-eight or seventy-two hours. The control reaction should not measure more than 3 mm. If the test is negative at the end of seventy-two hours, it is necessary to examine the area at intervals of several days, since a delayed reaction occasionally occurs.

TABLE 1. *Data on Skin Tests Employing Antigens of Bacterial and Viral Origin.*

TEST	MATERIAL EMPLOYED	TIME READ	SIZE OF POSITIVE REACTIONS	INTERPRETATION OF POSITIVE REACTIONS
Tuberculin	P. P. D. or O. T.	48 hr.	Edema and erythema greater than 5 mm.	Previous infection
Brucellergen	Brucellergen	48 hr.	Edema and erythema greater than 5 mm.	Previous infection
Chancroid	Vaccine (heat-killed bacilli)	48 hr.	Edema greater than 8 mm. and erythema greater than 14 mm.	Previous infection
Pertussis	Detoxified agglutinogen	15 min. and 24 hr.	Wheal in 30 min. or induration and erythema greater than 10 mm. in 24 hr.	Questionable immunity
Tularemia	Detoxified antigen	48 hr.	Edema and erythema greater than 10 mm.	Previous infection
Francis	Specific pneumococcus carbohydrate	15 min.	Wheal and erythema	Excess circulating antibody
Influenza-bacillus infection	Specific influenza-bacillus carbohydrate	15 min.	Wheal and erythema	Excess circulating antibody
Schick	Diphtheria toxin	48 and 96 hr.*	Edema and erythema greater than 10 mm.*	Susceptibility
Dick	Erythrogenic streptococcus toxin	24 hr.	Erythema greater than 10 mm.	Susceptibility to erythrogenic toxin
Frei	Inactivated lymphogranuloma-inguinale virus	48 hr.	Induration at least 5 or 6 mm.	Previous infection
Enders	Inactivated mumps virus	24 and 48 hr.	Erythema greater than 10 mm.	Immunity

*There is a great deal of variation in the literature as to what should be considered a minimal positive reaction. There is also variation as to when the test should be read.

Enders Test

Using as antigen a heat-inactivated suspension of the parotid gland of a monkey infected with the virus of mumps, Enders, Cohen and Kane[145] were able to demonstrate the development of dermal hypersensitivity in persons convalescent from mumps. In a systematic survey of almost 300 students at the Harvard Medical School a dermal reaction consisting of an area of erythema measuring at least 10 by 10 mm. was obtained in 96 per cent of those students who had a definite past history of mumps.[146] Of those who denied any previous infection, 50 per cent gave positive reactions. That these were not false-positive reactions is shown by the fact that 96 per cent of this group had mumps complement-fixing antibodies. This supports the suspicion based on epidemiologic grounds that inapparent mumps infection is not infrequent. I have observed 1 such case in a laboratory worker who was constantly exposed to mumps virus. She was known to have had no mumps complement-fixing antibodies and was skin-test negative, and hence was considered to be susceptible. Two months after she began working with the virus she complained of general malaise and ill-defined sensations in the left parotid gland. No salivary-gland involvement was discernible at any time. Shortly thereafter she developed complement-fixing antibodies and became skin-test positive.

Since mumps was observed only twice in several hundred persons who had a definitely positive skin test (an area of erythema greater than 10 by 10 mm. in twenty-four hours), it is clear that an inapparent infection will produce as solid an immunity as an overt attack. Accordingly, the demonstration of a positive dermal reaction with rare exception means immunity. In the last three years over 1500 skin tests have been performed without unpleasant local or general reactions of any description. Sixty-eight cases of mumps have been recorded in this group. In 57 of these there was either no dermal reaction or its area measured less than 2 by 2 mm. in diameter. In 8 cases areas were observed that ranged between 2 by 2 mm. and 10 by 10 mm. In only 3 cases was the area greater than 10 by 10 mm. If one accepts an area of erythema of 10 by 10 mm. or less as indicating susceptibility, then 95 per cent of those who eventually developed mumps were susceptible as determined by the intradermal test. Of several hundred persons who were found to have

reactions greater than 10 by 10 mm. in twenty-four hours, only 3 developed mumps.* It is therefore believed that a reaction greater than 10 by 10 mm. with rare exception means immunity against the mumps virus. The intradermal test is of no value as an aid in diagnosis, since the interval when a positive reaction is first observed may vary from several days to three months after the onset of the disease. Once hypersensitivity is established, it apparently persists for life.

Within the last few months the virus of mumps has been grown in the yolk sac of the developing egg embryo. This virus has been reported as giving reliable dermal reactions in immune persons.[147] Should this prove to be so, a cheap and ready source of virus for skin testing should shortly be available.

* * *

The pertinent data on the practical application of the tests discussed in this review are summarized in Table 1.

*False-negative tests have been observed in about 2 per cent of the persons considered to be immune on the basis of positive complement-fixation tests.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 31261

PRESENTATION OF CASE

A thirteen-month-old boy was admitted to the hospital because of the sudden appearance of a mass on the right side of the neck.

The child had been well until five weeks before admission, when he awakened one morning crying more than usual. The mother sensed that something was wrong, but the temperature was normal. At 11:00 a.m. the temperature had risen to 104°F. and the child was rushed to a hospital. A diagnosis of early pneumonia was made. He was given sulfadiazine, and the temperature returned to normal in two days. On the third hospital day an orange-sized mass suddenly appeared on the right side of the neck. This was aspirated, and the neck again appeared normal. X-ray examination demonstrated a mass in the upper mediastinum pressing on the trachea. There was no discharge from the site of aspiration, and no return of the swelling in the neck. On the seventeenth hospital day the child was discharged to his home, asymptomatic. Approximately two weeks later, with no recurrence of complaints, he was admitted to this hospital for further study.

The child had been delivered at term with no difficulty and without forceps. The birth weight was 7½ pounds. He was breast fed for only one week and thereafter, until eleven months of age, was maintained on an evaporated milk Dextri-maltose formula, adequately supplemented with vitamins. At one year he weighed 25 pounds. One week before the onset of the present illness he had one injection of diphtheria-tetanus toxoid.

Physical examination revealed a well nourished boy who was well developed for his age. He had a lusty cry and no apparent respiratory difficulty. He weighed 25½ pounds and measured 75 cm. in length. The skin was normal. The pupils were normal and reacted to light. Four incisors above and below, and a right lower premolar were present. There was abnormally profuse drooling of saliva from the mouth. The right side of the neck just above the clavicle was fuller than the left. A blunt, soft, smooth, oval, nontender mass about 4 cm. in diameter lay anterior to and appeared to merge with the right sternocleidomastoid muscle. This mass was thought not to move with swallowing. It presented no bruit or pulsation. The lungs were clear except for a few fine crepitant rales over the right upper lobe. The heart had normal position, size, rate, rhythm and sounds. The abdomen and extremities were normal.

The temperature, pulse and respirations were normal. The blood pressure was 105 systolic, 80 diastolic.

Examination of the blood showed a red-cell count of 4,200,000, with 12.2 gm. of hemoglobin, and a white-cell count of 13,600, with 70 per cent neutrophils, 28 per cent lymphocytes and 2 per cent monocytes. The urine was normal.

An x-ray examination of the chest showed a homogeneously dense mass in the right upper posterior chest that measured approximately 4 by 4 cm. in diameter (Fig. 1). It displaced the trachea to the right and anteriorly. There was no definite evidence of collapse of the upper lobe. The vertebral bodies and ribs showed no evidence of erosion. The heart shadow appeared to be normal. A barium swallow during fluoroscopy showed the esophagus to be displaced to the left by the mass both above and below the manubrium. Whether the esophagus was displaced backward or forward could not be determined.

The temperature, pulse and respirations and the appearance of the neck remained unchanged. The blood was grouped and crossmatched, and on the fifth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. NATHAN B. TALBOT: One may introduce the discussion of this case by commenting that, with the information at hand, it is not going to be possible to make anything more than a tentative diagnosis. Had we been given information concerning the nature of the fluid aspirated from the mass in the neck, it might have been easier to make a reasonably accurate diagnosis. Had the fluid removed when the child was seen first been replaced by some radio-opaque material, such as iodide solution, valuable information concerning the size, connections and geography of the mass might have been obtained. Transillumination of the cervical mass at that time might have been helpful, for it should have distinguished between blood and clear fluid. It would also have been of interest to know whether the cervical mass was reduced by gentle pressure and whether such a procedure prompted a change in the size of the thoracic mass. In other words it may be possible to make a fairly accurate preoperative diagnosis in such cases as this if advantage is taken of relatively simple procedures. Despite the paucity of information, certain possible diagnoses may be considered.

It seems probable that the mass in the neck was cystic, that the mass in the thorax was part of the same structure and that the mass was present prior

*On leave of absence.

to the episode of pneumonia, which perhaps through some mechanism induced a sudden increase in its size and hence called attention to its presence. It appears from the history that this lesion had not interfered seriously with the development of the child, since the measurements recorded are normal for an infant of his chronologic age. There was little to suggest that the process was inflammatory, since the temperature and pulse were not strikingly abnormal, and there was only a slight leukocytosis. Incidentally, no tuberculin test is recorded.

It is in this age group that congenital malformations frequently make themselves known. Of the cystic swellings of congenital origin that present in the anterior cervical triangle, branchial-cleft cysts and thyroglossal-duct cysts may be mentioned. Had the swelling presented in the posterior cervical triangle these could have been almost automatically ruled out. Although they cannot be completely discarded in the present case, I believe that they are unlikely diagnoses because of the fact that the cervical mass probably extended into or took origin in the posterior mediastinum. Incidentally, the mass did not move on palpation, which rules further against a thyroglossal duct.

May we look at the x-ray films?

DR. MILFORD D. SCHULZ: Here you see this rather sharply outlined mass in the right upper chest displacing the trachea anteriorly and to the left.

DR. TALBOT: Can we say it is a posterior mediastinal mass?

DR. SCHULZ: At least some of it lies posteriorly and displaces the trachea anteriorly as well as to the left, and one may assume that it arises outside the lung rather than in it.

DR. TALBOT: Can you see continuity of the mass in the chest with that of the neck?

DR. SCHULZ: It is difficult to be sure about the mass in the neck; there is no demarcation between the visible mass and any mass that may be present in the neck, for it is the same density as the normal soft-tissue structures of the neck.

DR. TALBOT: There are no sharp outlines and no shadows suggestive of teeth, bone or anything of that sort?

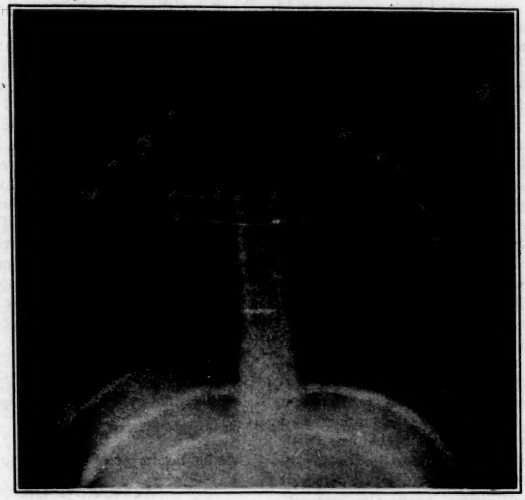

FIGURE 1. *Roentgenogram of Chest.*

DR. SCHULZ: No.

DR. TALBOT: If we assume that there was a posterior mediastinal mass, not apparently of pulmonary origin or at least not seriously impairing upper or lower respiratory function, we can discard the possibility of lung cyst. We are left with certain other possibilities.

The first of these is cystic hygroma, which is a cystic overgrowth of lymph channels due to a developmental disarrangement of the tissues. It often originates in the neck and may extend upward toward the ears or jaw or downward into the chest.[1] This diagnosis cannot be ruled out.

Secondly, one might consider the presence of a teratoma of mediastinal origin. These usually have a dense wall and occasionally show areas of calcification, although I gather they are less likely to

do so in this region than in other parts of the body.

The mass might have represented cystic degeneration of a variety of mediastinal tumors. It is said, however, that in such a lesion there is often some remaining solid and hence palpable tissue, which gives a clue to the diagnosis. No solid tissue was described in the present case.

Next the possibility arises that the mass was an arteriovenous aneurysm. The only finding in favor of this diagnosis is the blood pressure, which was slightly to moderately elevated. On the other hand the heart was of normal size, which rules quite strongly against this diagnosis. It also seems most unlikely that blood was aspirated from the mass, since no mention of such a potentially important fact was made. A deeply seated hemangioma would also yield blood on aspiration.

There remains one other interesting possibility, an esophageal duplication or mediastinal cyst of enteric origin.[2] These may be silent for a period of time but are usually recognized during infancy. Cough, dyspnea, cyanosis and recurrent or chronic pneumonia are the usual presenting complaints and when present are due to pulmonary compression. Dysphagia and regurgitation of feedings occur when there is impingement on the esophageal lumen. In this connection it is of interest that the child was said to drool abnormally. Although this seems an extraordinary remark when applied to an infant of this age, it may have been inserted to provide us with a clue or — and such would not be unique in these meetings — as a sort of red herring. Incidentally, pain such as this patient apparently had at the onset of the illness may be caused by distention of the walls with suddenly increased intracystic pressure. In such cystic structures, infection such as this patient had may in some manner lead to obstruction of the normal lymph channels, with consequent rapid enlargement. Finally, the x-ray findings are characteristic of a posterior mediastinal tumor or cyst. Fluoroscopy, as in this patient, shows no fistulous connection. Although they occasionally erode the vertebras, there was no evidence of that here.

In conclusion it is fair to say that the most important point in such a case as this is that surgical exploration should be carried out for the purposes both of an accurate diagnosis and of potentially corrective procedures. I should place mediastinal cyst of enteric origin as my first choice, and cystic hygroma as my second.

Dr. Benjamin Castleman: Dr. Sweet, you operated on this child. Will you describe your findings?

Dr. Richard H. Sweet: This was an amazing tumor in many ways. My preoperative diagnosis was a cyst of enteric origin, the so-called "reduplication" that Dr. Ladd talks about. I know enough about mediastinal tumors to appreciate that one can rarely make an accurate diagnosis ahead of time. The fluid aspirated from the cyst within the neck was reputed to have been clear. That information obviously was not in the case history as presented.

The tumor was filled with cystic loculations, which contained watery fluid. It was an enormous tumor, considering the size of the child. Anatomically it covered a large surface, and in freeing it we disclosed a great many structures. The operation was a lesson in anatomy. It extended to the azygos vein and right main bronchus. Posteriorly it was necessary to denude the first and second ribs, the actual rib periosteum being removed with the tumor. It was an adherent tumor, and in taking it out we exposed and divided the first intercostal nerve and the highest intercostal artery, which are rarely seen. When we dissected the tumor medially we found that, although it was not an invasive tumor, it at least had surrounded all the structures and had grown around the innominate vein and innominate artery. In order to get the subclavian artery and other structures away from it I had to incise the tumor and peel it off one side one way and the other side another way. In doing that I exposed the right vagus nerve and the right recurrent laryngeal nerve and the cords of the brachial plexus as they crossed over the first rib. It was also adherent to the esophagus, and there was a portion of it that extended to the left behind the heart and great vessels, which I did not get. There was a portion within the neck, which I could not possibly remove because it had grown around all the structures there and I could not dissect beyond the confines of the superior portion of the chest.

Clinical Diagnosis

Mediastinal cyst of enteric origin.

Dr. Talbot's Diagnosis

Mediastinal cyst of enteric origin.

Anatomical Diagnosis

Hygroma colli cysticum.

Pathological Discussion

Dr. Castleman: Dr. Sweet has outlined extremely well the gross penetrating character of the tumor. Microscopically this same feature was evident. The tumor was composed of multilocular cystic spaces of varying sizes, all of which were lined with flattened endothelial cells, namely, the structure of lymph vessels. It was then a true cystic hygroma, which is a form of lymphangioma and apparently arises from lymphatic rests, derived from the jugular lymph sac. Scattered in between some of the cystic spaces were many large nerves and blood vessels, which were apparently being surrounded and engulfed. This appearance is in keeping with Goetsch's[3] exhaustive study of these hygromas. He showed that they grow and propagate by the sprouting from the cyst walls of endothelial-lined membranes that

continue to secrete and form more cystic spaces, and so on. As it continues to grow, it engulfs muscles, nerves and blood vessels, which accounts for the operative findings in this particular case. In Goetsch's series of 12 cases most of the tumors were in the neck and had not invaded the mediastinum. He also made the statement that the prognosis is poor in those cases in which the tumor goes down in the mediastinum. One case in his series responded well to x-ray treatment, so that perhaps it would be worth while to give the patient postoperative x-ray treatment.

DR. SWEET: It was obvious to me when I had exposed the tumor and had begun the dissection that it was one that could not be totally removed.

DR. TALBOT: What was the postoperative course?

DR. SWEET: The patient made an excellent recovery and went home. The only evidence of the operation, except for the scar, is that he has a Horner's syndrome.

DR. CASTLEMAN: But you expected that after the operation.

DR. SWEET: Yes; I wrote it in my operative note that I had interrupted the sympathetic chain, the intercostal artery and the first intercostal nerve.

DR. SCHULZ: When giving x-ray treatment it should be borne in mind that one might destroy the epiphyseal growth in a child of this age.

DR. CASTLEMAN: Has the child any symptoms of a mediastinal tumor?

DR. SWEET: No.

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CASE 31262

PRESENTATION OF CASE

A seventy-two-year-old man was brought to the hospital because of hematemesis, tarry stools and a loss of consciousness.

About fifteen years before entry the patient began to suffer financial reverses and developed abdominal symptoms, which were attributed to a peptic ulcer. Ten years before admission he was treated at another hospital for a bleeding ulcer. He followed the prescribed diet sporadically and acquired such poor eating habits that four years later he was again admitted because of quite marked skin and other systemic changes consistent with severe nutritional deficiency. He responded well to an improved dietary regime but continued with periodic and vague epigastric symptoms, which included mild distress and a feeling of marked gaseous distention after meals. Four years before admission he passed tarry stools for two weeks. He was treated at home with bedrest and a bland diet. From then until the time of admission to this hospital he had continued on a fairly well supervised, bland diet. Three and a half years before entry a gastrointestinal series showed a constant deformity at the base of the duodenal cap near the pyloric sphincter, with an ulcer at this point measuring 6 mm. in its greatest diameter. Another gastrointestinal series a month later showed some decrease in the size of the ulcer. A year later, or two years before admission, another gastrointestinal series showed a small 1-mm. ulcer niche, which was probably on the lesser curvature side at the pylorus. There was some deformity of the duodenal cap. Three days before admission he vomited a cupful of coffee-grounds fluid and began to have loose tarry stools, with increased epigastric pains. On the day of entry he fainted shortly after complaining of pain in his left leg. On regaining consciousness he complained of weakness and cold perspiration. Six years before admission he began having pain in the arms radiating to the shoulders. These pains came on when he walked in a cold wind or at the onset of any exertion. When severe this pain was promptly relieved by nitroglycerin. At that time the blood pressure was 158 systolic, 100 diastolic. Four years before admission he complained of substernal oppression on exertion, with less pain in the arms and shoulders. The blood pressure was 145 systolic, 85 diastolic. During the four years before admission, the substernal pains varied in frequency and severity. They were worse in cold, damp or extremely hot weather. Nitroglycerin for severe pains and barbiturate sedation continually afforded considerable relief. A long blowing systolic apical murmur was unchanged during the six years before entry. The heart size was consistently thought to be on the upper limit of normal by percussion and auscultation. The pulse was 75 to 80 and regular, and the blood pressure was quite constant at about 140 systolic, 80 diastolic. An electrocardiogram three months before admission showed a normal rhythm with a rate of 85, sagging ST_1 and ST_2, inverted T_1, diphasic T_2, low upright T_3, wide slurred QRS complexes measuring 0.14 to 0.16 second, occasional ventricular premature beats, deep S_2, small R in Leads CF_2 through CF_4, notched or bifid upright QRS in Lead CF_5, upright T waves in Leads CF_2 through CF_4 and inverted T waves in Lead CF_5.

Physical examination revealed a well developed, fairly well nourished man. The chest was moderately emphysematous. The skin was pale, cold and clammy. He was stuporous but was able to obey commands. There was a sagging but not a complete paralysis of the left face, and no apparent paralysis of the extremities. The lungs were clear. No heart sounds could be heard. The heart was not enlarged to percussion. The abdomen was soft, slightly tympanitic but not markedly distended; peristalsis

was diminished. The liver and spleen could not be felt.

The temperature was normal, the pulse not obtainable, and the respirations were 25. The blood pressure was not obtainable.

Examination of the blood showed a red-cell count of 1,960,000. After two whole-blood transfusions the red-cell count was 3,600,000, and the white-cell count 10,700, with 66 per cent neutrophils. A glove specimen of stool was tarry and gave a ++++ guaiac test. Blood drawn after the transfusions showed a serum nonprotein nitrogen of 94 mg. per 100 cc., a fasting blood sugar of 137 mg. and a protein of 6.4 gm.

During the first twenty-four hours the blood pressure was periodically obtainable and rose on one occasion to 85 systolic, 50 diastolic. After the first twenty-four hours, despite whole-blood transfusions, the blood pressure was only rarely obtainable, reaching 100 systolic, 65 diastolic, on one occasion. The pulse was extremely weak when obtainable and remained between 80 and 100. During the first twenty-four hours he complained of epigastric and low substernal pain. He had no bowel movements and did not vomit. A Levine tube afforded relief from gaseous distention and abdominal discomfort. It brought up a small amount of blood in about 500 cc. of thin gastric contents. The urine gave + to ++ tests for albumin; the sediment showed an occasional red and white cell and a few hyaline casts.

Early on the second day the patient was digitalized with Cedilanid. An electrocardiogram a few hours later showed normal rhythm, at a rate of 120, a PR interval of 0.22 second, inverted T_1, upright T_2 and T_4 with slurred QRS complexes that measured 0.12 second, small R and deep S waves in Leads CF_2 through CF_4 and upright wide QRS in Lead CF_5 with inverted T waves. The blood pressure and pulse were again not obtainable near the end of the second day. The lungs were filled with rales, and the liver was enlarged.

The patient became cyanotic and comatose and expired quietly approximately forty-eight hours after admission.

Differential Diagnosis

Dr. David Hurwitz: We are dealing with an elderly man whose history points to both severe gastrointestinal and cardiovascular disease. He had had ulcer symptoms for fifteen years and gastrointestinal bleeding off and on for ten years. X-ray confirmation of the ulcer was obtained three and a half years before entry, and subsequent x-ray examination showed evidence of healing. The last gastrointestinal series, two years before admission, demonstrated the presence of an ulcer that seems to have been in a somewhat different location than the one originally described. Are these films available?

Dr. Milford D. Schulz: This 5-mm. fleck probably represents the ulcer crater that was described; it appears to be in the base of a severely deformed duodenal bulb, but it is difficult to be certain where the pylorus is. On the examination a month later the crater is slightly smaller. On the last examination a quite small ulcer is seen that occupies a position comparable to that previously described.

Dr. Hurwitz: For the final two years there is no record of further gastrointestinal bleeding or distress until three days before entry, when he vomited blood and passed tarry stools. I think that the evidence for a bleeding peptic ulcer is excellent. The long duration of the recurrent hemorrhages and the x-ray evidence make ulcer by far the best possibility. The duration, x-ray findings and apparent freedom of significant symptoms for two years are certainly against neoplasm. There is also nothing pointing to bleeding esophageal varices.

In addition to the ulcer symptoms he had a six-year history of exertional substernal pain relieved by nitroglycerin. I think that we may call this angina without much question. "Pain in the arms radiating to the shoulders" is unusual, but later the symptoms became more typical. The blood pressure was not remarkable for his age. The electrocardiogram showed definite evidence of myocardial disease. From the description, I take it that he had left bundle-branch block. From the history and electrocardiogram, then, we can say that he had coronary heart disease.

On admission, he appears to have been in shock. His face showed "a sagging but not a complete paralysis of the left face." It is difficult to ascribe much significance to this in such an acutely ill patient. There is no further mention of pain in the leg. I assume that it did not recur. Apparently he remained in shock until death, in spite of transfusions.

The positive laboratory findings are, first, a severe anemia, which was improved by transfusions, and, secondly, an elevated nonprotein nitrogen. The latter is a frequent finding in cases of severe bleeding into the gastrointestinal tract. It occurs within twenty-four hours of the bleeding and, when markedly elevated, is considered to be a poor prognostic sign. Whether the elevation of the nonprotein nitrogen is due solely to absorption of blood from the intestinal tract or to the effects of acute blood loss, dehydration, shock and poor renal function is not clear. Perhaps a combination of all these factors is present. A blood sugar level of 137 mg. per 100 cc. is ordinarily suggestive of diabetes but is not particularly significant in an elderly patient in shock who possibly was given some intravenous glucose with his transfusions during the preceding night. The urinary findings are consistent with what one would expect in a patient in shock. The electrocardiogram after Cedilanid shows a prolonged PR and a prolonged QRS, although the latter was

shorter than it was before entry. These findings are indicative of coronary disease, without pointing toward an acute process.

Severe hemorrhage from an ulcer that has eroded a sclerotic vessel can produce the major clinical picture alone. No added condition is necessary. It is interesting, however, to speculate on what effect, if any, the severe hemorrhage had on his coronary heart disease. It is known that severe blood loss may further increase coronary insufficiency and may result in irreversible myocardial changes, which, if of sufficient duration, may result in myocardial infarction. Is there any evidence of this having occurred here? He did have substernal pain after entry, but it was low and associated with epigastric pain that occurred before his collapse and was probably due to the ulcer. The final electrocardiogram did not give any evidence of an acute process, although it was taken early and the patient was in shock. It is quite possible that he had a fresh infarction on the basis of pre-existing coronary disease and shock, but I cannot make the diagnosis on the available data.

It is difficult to evaluate the history of pain in the left leg before entry. Leg pain followed shortly by collapse and subsequent substernal and epigastric pain suggests a dissecting aneurysm. The lack of antecedent hypertension, the absence of severe chest or back pain and the short duration of the leg pain, however, are against this diagnosis. Usually in this condition the blood pressure remains high after dissection takes place, and a few cases present the picture of collapse without pain. On the whole, it is not likely that the patient had a dissecting aneurysm, and I prefer to leave the leg pain unexplained.

In summary, then, I should say this patient had severe gastrointestinal bleeding from a duodenal ulcer, which had probably eroded a sclerotic vessel. This alone can explain practically the whole picture. In addition, this patient had had clinical evidence of coronary heart disease for some time before the onset of the hemorrhage. The shock might have been responsible for a fresh myocardial infarction, but we have no clinical evidence for it.

Dr. Benjamin Castleman: Dr. Williams, have you anything to add?

Dr. Conger Williams: Bundle-branch block often obscures changes in the electrocardiogram that have been produced by myocardial infarction. This is especially true in left bundle-branch block complicated by anterior myocardial infarction, because both conditions result in the loss of R waves over the precordium in Leads 1 to 4. Sometimes the diagnosis can be made by observing serial changes in the T waves. In this case the electrocardiogram does not help in making the diagnosis beyond indicating likely damage to the coronary circulation, which could have been chronic.

Dr. Chester M. Jones: A high nonprotein nitrogen level is always interesting when associated with hemorrhage. It is important, however, not to lay too much stress on it. It was believed for some time that a high nonprotein nitrogen associated with hemorrhage, as Dr. Hurwitz has pointed out, is a bad prognostic sign. It actually does not work out that way. We have seen them even higher than this and the patients do well.

Clinical Diagnoses

Duodenal ulcer, bleeding.
Coronary heart disease.
Coronary thrombosis, recent?

Dr. Hurwitz's Diagnoses

Duodenal ulcer, with erosion of sclerotic vessel and hemorrhage.
Coronary heart disease, possibly with recent myocardial infarction.

Anatomical Diagnoses

Peptic ulcer, bleeding.
Coronary thrombosis, recent and old.
Myocardial infarction, early and old.

Pathological Discussion

Dr. Castleman: The autopsy findings were almost exactly as Dr. Hurwitz predicted. This man had a peptic ulcer that bled before he came into the hospital. There was evidence that the bleeding had stopped while he was in the hospital, because we found no blood in the stomach. There was, however, old blood throughout the intestinal tract. The ulcer involved the pylorus.

The heart weighed 500 gm. and showed severe sclerosis of the coronary arteries, such as one sees in patients with angina. There was an old occlusion of the right coronary artery, which must have occurred years previously, with resultant scarring of the posterior wall of the left ventricle. In addition there was a terminal acute coronary thrombosis in the left descending artery and an associated acute anterior myocardial infarction. The myocardium showed acute degeneration of the fibers with polymorphonuclear infiltration, the picture that one sees in the early stages of myocardial infarction.

Dr. Jones: Was there arteriosclerosis of the arteries in the leg, which caused the pain?

Dr. Castleman: He had generalized arteriosclerosis. There were no thrombi in the leg veins and no evidence of pulmonary infarction.

There was also an extensive terminal bronchopneumonia, which must have occurred during the last day or two. The final blow was the coronary thrombosis.

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PROPHYLAXIS AND TREATMENT OF GAS GANGRENE

There was a great deal of optimism in the earlier part of the war about the relatively small number of cases of gas gangrene encountered in the various theaters where the British and American troops were operating. It was assumed that the widespread use of sulfonamide drugs locally and systemically was responsible for the low morbidity from this disease. Experimental studies on the use of these drugs in the prevention of infection in animals also served to strengthen this belief. As the fighting moved into European countries, however, cases of gas-gangrene wound infection have become of increasing importance.[1] The problem has been reviewed by the Medical Research Council in England,[2] and has been brought up to date more recently in a supplement of the *Army Medical Department Bulletin* issued by the British War Office.[3] Most of the significant clinical features of this condition are brought out in the latter publication, including some that are not widely appreciated. Recommendations are also given for the use of sulfonamides, penicillin and antitoxins, both for prophylaxis and for the treatment of established infections. These recommendations are based on recent experiences. A few excerpts from this bulletin and a résumé of the recommendations for treatment should be of interest to American readers.

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> Gas gangrene (clostridial myositis) may be defined as an infection of muscle with anaerobic bacteria of the genus Clostridium (particularly, *Cl. welchii*, *Cl. oedematiens* and *Cl. septicum*), whose common habitat is in soil and in the intestines of many animals. These organisms produce powerful toxins which, by their necrotizing action, favor the local spread of infection and by their wider dissemination in the body rapidly produce a profound and shocklike toxemia. The mere finding of anaerobic bacteria in a wound of muscle is of little significance; in warfare over cultivated ground almost every wound will be so contaminated. In contrast to simple contamination, anaerobic infection of muscle is a true myositis, always acute and usually diffuse. Sometimes only a single muscle is involved, but as a rule whole muscle-groups are affected. The disease is extraordinarily acute, and can rapidly spread through an entire limb. It is this fulminating course that makes gas gangrene so dangerous, and renders its early and accurate diagnosis of such extreme importance.
>
> The essential features in its prevention and treatment are the elimination of the bacteria by excision of the infected tissues and by chemotherapeutic drugs, and the neutralization of the toxins by the administration of antitoxins. The disease has a very high death-rate unless it is promptly diagnosed and properly treated. . . .
>
> Gas gangrene can follow quite trivial injuries, but is most likely to develop where the wound is associated with the following features: interference to the main blood-supply of a limb; extensive laceration of muscle, particularly of the thigh, buttock and shoulder; compound fractures of the long bones, especially [those] of the lower limb; foreign bodies, clothing or dirt carried deeply into the tissues; prolonged application of a tourniquet, or tight packing; application of a tight plaster or even a tight dressing to an inadequately excised wound; delay in surgical treatment.

In the prophylaxis of gas gangrene it is recommended that the following measures be taken as soon as possible after infliction of the wound: one ampule containing 22,500 units of polyvalent gas-gangrene antitoxin should be immediately injected intravenously or intramuscularly, preferably by the

former route, together with the usual dose of tetanus antitoxin* (if there is a delay of more than twenty-four hours, 45,000 units—two ampules—should be given); sulfonamide drugs should be administered both locally and systemically (the British also include a 1 per cent suspension of finely powdered proflavine in sulfathiazole for local use, but the efficacy of all local chemotherapy has been questioned by American surgeons); adequate wound excision should be provided (this is the most valuable prophylactic measure and should *never* be unnecessarily delayed).

In the treatment of established gas gangrene, surgical measures are combined with antitoxin and drugs, speed being essential to the saving of life. Preoperatively it is recommended that 67,500 units (three ampules) of polyvalent gas-gangrene antitoxin, or 112,500 units (five ampules) if toxemia is severe, be injected, preceded or accompanied by sulfathiazole (sulfadiazine would probably be preferred in this country). The soluble form of the latter may be given subcutaneously in salt solution or intravenously either in saline or in distilled water (it is important not to give sodium salts of sulfonamide drugs in the same apparatus used for blood transfusion since clots may form). Transfusions of whole blood are advised unless particularly contraindicated. Pentothal, followed by nitrous oxide and oxygen (40 to 50 per cent), is recommended for anesthesia. Anoxia should be guarded against during the inhalation anesthesia.

> Removal of the infection by complete excision of the affected tissues is essential. Amputation is by no means a routine necessity, though frequently inevitable because of vascular damage. Where only one muscle or one group of muscles is involved, that muscle or muscle-group should be extirpated from origin to insertion. An ample exposure is necessary, and great care must be taken not to damage the blood supply to adjacent muscles. . . .
>
> If radical surgery is impossible, either because of the site of the infection or the condition of the patient, the muscle-sheaths and muscles should be freely incised to relieve tension, and intensive therapy with antitoxin and drugs pursued. Where a limb is involved, it is frequently of advantage to apply a tourniquet proximal to the upper limits of infection in order to establish a "physiologic amputation."

For local chemotherapy it is recommended that the wound should be washed out if necessary with a 0.1 per cent solution of proflavine and then frosted with a sulfonamide.

Penicillin therapy is also recommended. The initial dose (30,000 units) is given intramuscularly on the operating table or earlier. This is followed either by a slow intravenous drip at the rate of 5000 or 6000 units per hour for twenty-four to forty-eight hours or by the injection of 15,000 units every three hours. Larger doses, up to 25,000 units every two hours, are probably preferable.

It is best to give blood transfusions and glucose-saline infusions by drip during the following twenty-four to forty-eight hours. Antitoxin administration is continued so long as signs of toxemia remain. A dose up to 60,000 units, repeated every four to six hours, may be given by intravenous injection in a small volume. The reduction in the pulse rate is taken as evidence of diminishing toxemia. Sulfonamide therapy is continued by parenteral route so long as necessary and orally thereafter, adequate amounts of alkali being given and the fluids being adjusted to avoid renal complications.

It is of interest that Dowdy, Sewell and Vincent,[4] on the basis of extensive studies on gas-gangrene infection in experimental animals, have also come to the conclusion that all these measures should be used.

With respect to sulfonamide treatment, interest has recently centered about the German preparation known as Marfanil. This compound is 4-aminomethyl-benzene sulfonamide and is of particular interest because its action is said not to be inhibited by *p*-aminobenzoic acid, serum or pus. Although the compound has been known in this country for at least three years, it did not receive much attention until it was found by the British among German supplies captured in North Africa.[5, 6] Marfanil is highly soluble and, in preliminary clinical trials, appears to be somewhat more effective than the earlier preparations for local use in the prevention and treatment of anaerobic wound infections. These findings have not been widely confirmed, nor is the toxicity of the compound well understood. When given by mouth it apparently is no more effective than sulfanilamide. Further studies of this compound and related ones would be of interest, but since the use of penicillin is now occupy-

*The British Medical Corps still recommends the routine prophylactic use of tetanus antitoxin in spite of the fact that many British soldiers have been immunized with tetanus toxoid.

ing the attention of most workers, the clinical trial of these chemicals outside Germany will undoubtedly be delayed.

That considerable difference of opinion exists concerning the prevention and treatment of gas gangrene is evidenced by a recent directive issued by the War Department.[7] This bulletin does not recommend the prophylactic use of gas-gangrene antitoxin and questions its therapeutic value, except the employment of trivalent serum, containing *Cl. oedematiens* antitoxin, in cases of the "wet" type of infection. Furthermore, although the administration of sulfonamides and penicillin is advised, it is stated that any form of chemotherapy probably does little more than to prevent the spread of infection. Chief reliance is placed on proper surgical management.

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MASSACHUSETTS MEDICAL SOCIETY

DEATHS

COX — Oscar F. Cox, M.D., of Brookline, died June 3. He was in his fifty-eighth year.

Dr. Cox received his degree from Tufts College Medical School in 1914. During World War I he served with the Army overseas. He was a member of the staff of Massachusetts Memorials Hospitals and the Boston Dispensary. He was chief of the Genitourinary Clinic at Boston Dispensary, director of the Division of Genitoinfectious Diseases at Massachusetts Memorial Hospitals, chairman of the Advisory Committee on Venereal-Disease Control of the Massachusetts Department of Public Health, director of the Massachusetts Society for Social Hygiene, secretary of the American Neisserian Medical Society and a member of the Subcommittee on Venereal Diseases of the National Research Council. He was clinical professor of urology at Tufts College Medical School and associate professor of medicine at Boston University School of Medicine. He was a fellow of the American Medical Association.

His widow, his mother, a son and a daughter survive.

WHELAN — Charles Whelan, M.D., of North Cohasset, died May 29. He was in his sixty-ninth year.

Dr. Whelan received his degree from Tufts College Medical School in 1905. He was among the first sixteen of its graduates to enlist in the medical corps during World War I, and organized the x-ray department at the debarkation hospital in New York where 38,000 casualties were treated. He had been chief radiologist at the Quincy City Hospital for several years and was consultant in roentgenology at the Carney Hospital and New England Hospital for Women and Children. He was a member of the American Board of Radiology, the New England Roentgen Ray Society and the Radiological Society of North America and a fellow of the American Medical Association.

His widow and two daughters survive.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

SMITH — Henry O. Smith, M.D., a lifelong practitioner in Hudson, died suddenly on May 14, 1945, just after he had completed a visit at a patient's home in Londonderry. He was born in Hudson on December 18, 1864, graduated from Dartmouth College in 1886 and received his medical degree from Bellevue Hospital Medical College in 1887. He started practice in Hudson in 1888 and for the past fifty-seven years had continued the practice of medicine there.

Dr. Smith was a member of the county and state medical societies, having served as speaker of the House of Delegates of the New Hampshire Medical Society in 1925–1926, as president of the state society in 1929–1930 and as a member of the Board of Trustees from 1933 to 1942, when he was elected trustee emeritus.

He was presented the Gold Medal of the state society for fifty years' membership at the meeting in 1938, and that same year he was honored at a testimonial dinner by his townspeople, who presented him with a suitably engraved watch "in appreciation of fifty years of faithful service."

Dr. Smith was a member of the Hudson Baptist Church, Hudson Grange, New Hampshire Historical Society and New England Historical Genealogical Society.

A number of years ago he wrote the history of the Baptist Church of Hudson, and in 1927 he compiled and published *The Early Story of Hudson, New Hampshire*. He served as chairman of the committee to formulate plans for the observance of the one hundred and fiftieth anniversary of the New Hampshire Medical Society. Along with this work, he edited, amended and brought up to 1941 *The Story of the New Hampshire Medical Society*, which originally had been written, including the facts up to 1854, by Dr. L. Bartlett How. This was printed and distributed to the members of the state society.

Dr. Smith is survived by one son, Dr. Deering G. Smith, of Nashua, two grandchildren and one sister.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

NEW TYPE STANDARD DEATH CERTIFICATES

Under the General Laws, Chapter 46, Section 10, a physician or officer furnishing a death certificate shall insert a recital and specify the war, if the deceased is a veteran.

Secretary of State Frederic W. Cook has directed that there be printed on the reverse side of the Standard Death Certificate the following:

Date of entering military service
Date of discharge
Rank, rating
Organization, outfit and service number

Dr. Vlado A. Getting, commissioner of the Massachusetts Department of Public Health, has called to the attention of the boards of health of the Commonwealth that the Standard Death Certificate is not complete until the data called for, as to the veteran, is recorded thereon.

PENICILLIN FOR TREATMENT OF GONORRHEA

Penicillin is now available without cost to all physicians of the Commonwealth for the treatment of gonorrhea.

Physicians are requested to submit a report of the case of gonorrhea on the form supplied by the Massachusetts Department of Public Health for that purpose. A supply of these forms will be sent on request.

Two bottles of penicillin, each containing 100,000 Oxford units, may be requested for each case. Directions for administration of the penicillin are enclosed with each bottle.

Points of distribution outside of the Metropolitan Boston Area are located at the State Co-operating Venereal Disease Clinics. Otherwise the penicillin request should be made to the Antitoxin and Vaccine Laboratory, 375 South Street, Jamaica Plain. Requests should be submitted to the nearest point of distribution.

For further information call the Division of Venereal Diseases, Department of Public Health, State House, Boston (CAPitol 4600).

MISCELLANY

NEW DEAN AT DARTMOUTH MEDICAL SCHOOL

Dr. Ernest M. Hopkins, president of Dartmouth College, recently announced the appointment of Dr. Rolf C. Syvertsen as dean of the Dartmouth Medical School, effective with the start of the new academic year on July 1. Dr. Syvertsen succeeds Dr. John P. Bowler, who, although he has resigned his administrative post, will continue on the medical faculty as professor of surgery.

Dr. Syvertsen, a graduate of Dartmouth in the class of 1918, will remain on the faculty as professor of anatomy. He was named assistant dean of the medical school last June, after filling the position of secretary for twenty years. He joined the medical school faculty in 1923, after serving as assistant in biology and zoology in the college for two years. He obtained his M.D. degree from Rush Medical College in 1936 and has held his professorship in anatomy since 1938.

NEED FOR RED CROSS HOSPITAL WORKERS

Recognition of the outstanding contribution social workers are making in healing the emotional wounds of war has resulted in an unprecedented demand for their services.

The American Red Cross needs 750 trained social workers at once for supervisory, administrative and staff positions in military hospitals, largely in the United States. The wounded and disabled returned to this country for further treatment need the skilled help of trained and experienced social workers. New and higher salary schedules, ranging from $170 to $350 monthly, depending on education, experience and job assignment, have been adopted by the Red Cross. Quarters are provided, and if not available at the hospital, an additional allowance is made. Free uniforms are also issued.

In addition, 1650 untrained and partially trained workers are needed by the Red Cross to serve in the area of social case work under professional guidance. Salaries range from $140 to $200 monthly. The hospital program also calls for 600 recreation workers at monthly salaries of $150 to $325.

The project for which these 3000 hospital workers are being recruited will continue for many years. Despite this, however, employment will be offered by the Red Cross to any qualified worker willing to serve a minimum of one year: Applications should be filed at the nearest of the Red Cross area offices, which are as follows: North Atlantic Area, 300 Fourth Avenue, New York 10, New York; Eastern Area, 615 North St. Asaph Street, Alexandria, Virginia; Southeastern Area, 230 Spring Street, N. W., Atlantic 3, Georgia; Midwest Area, 1709 Washington Avenue, St. Louis 3, Missouri; and Pacific Area, Civic Auditorium, Larkin and Grove streets, San Francisco 1, California.

NOTES

At its meeting on May 18, the New England Roentgen Ray Society paid honor to its distinguished member, Dr. George W. Holmes, pioneer radiologist and teacher, by establishing an annual lecture to be known as the George W. Holmes Annual Lecture.

Dr. Wesley Bourne of McGill University, Montreal, Canada, will deliver the first of the annual series of Osler Lectures of the University of Vermont College of Medicine at the Fleming Museum, Burlington, Vermont, July 5 and 6, at 8 p.m., and July 7, at 10 a.m. His subject will be "Anesthesia: Some contemplations."

CORRESPONDENCE

DEPRIVATION OF LICENSES

To the Editor: At a meeting of the Board of Registration in Medicine held June 6, the Board took the following actions:

To revoke the license of Dr. Julius Shubert, 45 McLean Street, Boston, to practice medicine for not less than three years because of gross misconduct in the practice of his profession as shown by collusion.

To suspend the license of Dr. Pasquale E. Massa, 232 Hanover Street, Boston, to practice medicine for a period of one year because of gross misconduct in the practice of his profession as shown by violation of the narcotic law and conspiracy to violate this law.

H. Quimby Gallupe, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

RESTORATION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held June 6, the Board voted to restore the license to practice medicine in this Commonwealth of Dr. Ralph K. Coleman, 25 Fessenden Road, Arlington (formerly of Lowell).

H. Quimby Gallupe, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

THE FLINT FAMILY

To the Editor: In a letter published in the May 3 issue of the *Journal*, I made the suggestion that the Austin Flint referred to in the anecdote by the Reverend George Allen might have been a connection or even an ancestor of the two famous Austin Flints of New York City.

I have since learned that the latter is true and that Austin Flint, of Leicester, was the grandfather of the younger Austin Flint of New York City. The line is as follows:

Dr. Edward Flint, of Shrewsbury
|
Dr. Austin Flint, of Leicester (1760-1850)
|
Dr. Joseph H. Flint, of Leicester (1786-1846)
|
Dr. Austin Flint, of New York (1812-1886)
|
Dr. Austin Flint, of New York (1836-1915)

There were at least eight physicians in this family, and several of them lived to be ninety years of age, including Edward Flint, of Leicester, also a son of Austin Flint of Leicester.

A. E. P. Rockwell, M.D.

Shrewsbury, Massachusetts

GIFTS OF MEDICAL BOOKS AND JOURNALS URGENTLY NEEDED FOR CZECHOSLOVAKIA

To the Editor: The Czechoslovak medical libraries and laboratories have been plundered by the Germans, and their research material wantonly destroyed. For the past six years no knowledge of the remarkable progress of American medicine has reached Czechoslovakia to benefit its people. Therefore a complete library of recent American medical literature is needed at the Charles University in Prague, as well as other universities and institutions. All publications since 1938 will be particularly welcome.

Any person or organization wishing to contribute is asked to communicate with the Secretary, American Friends of Czechoslovakia, 355 Boylston Street, Boston 16, or with the Masaryk Institute, 8 West 40th Street, New York City 18, which as a depositary for Charles University in Prague receives and files donated publications.

MRS. J. PHILIP LANE, *Secretary*
American Friends of Czechoslovakia
353 Boylston Street
Boston 16

BOOK REVIEWS

The Religious and Philosophical Aspects of Van Helmont's Science and Medicine. By Walter Pagel. 4°, paper, 44 pp. Baltimore: The Johns Hopkins Press, 1944. $1.00. (Supplements to the Bulletin of the History of Medicine. Editor: Henry E. Sigerist, M.D.)

This book, written by an experienced historian of medicine, makes a valuable contribution to the further understanding of that great medical figure Johannes Baptista van Helmont, the *per ignem Philosophus*. Students of medicine must come to this book prepared for a hard intellectual feast, for it is not easy reading; they will, however, be repaid for their effort.

The research activities of van Helmont show a close interdependence of religious belief, philosophical outlook and scientific achievement. Modern students would do well to pry themselves free occasionally from the present-day sharp cleavage between science and religion to read of the works of a scientist who lived in an atmosphere where religious conviction constituted a strong incentive to scientific work, where only the God-fearing believed they could attain the art of prolonging life and where religious pragmatism was the driving force to medicine as the ultimate aim of science, all of which brings to mind the names of Pasteur, Charles Bell and Darwin. The author succeeds in showing why van Helmont, who introduced the concept of "gas," who designed scientific instruments, who used the balance in scientific quantitative experiments, who discovered acid as the principle of digestion in the stomach and laid the foundations for biochemistry and pathology, could deprecate sheer reasoning (*Ratio*) as a means for the investigation of life.

The book is provocative and should be in all medical libraries.

The Gastro-Intestinal Tract: A handbook of roentgen diagnosis. By Fred J. Hodges, M.D. 8°, cloth, 320 pp., with 130 plates. Chicago: The Year Book Publishers, Incorporated, 1944. $5.50.

This is one of a series of books on roentgen diagnosis. It is short but represents a careful summary of the present knowledge of the gastrointestinal tract as determined by roentgenologic methods. The descriptive text shown on the left-hand pages is conveniently placed opposite excellent reproductions on the right. The text is brief, but within it is a large amount of useful information. There is a short but well-chosen bibliography at the close of each chapter. It should be of value to the student and also to the practitioner.

Fertility in Women: Causes, diagnosis and treatment of impaired fertility. By Samuel L. Siegler, M.D. With a foreword by Robert L. Dickinson, M.D. 8°, cloth, 450 pp., with 194 illustrations. Philadelphia: J. B. Lippincott Company, 1944. $4.50.

This book is divided into eleven chapters. The first deals with human fertility, the incidence of barrenness and the historical treatment. The second discusses the methods of evaluating and investigating fertility. The history is the subject matter of the third chapter, which also discusses the causes of sterility, acquired and inherent, and points the way to the detailed investigation of the subject. The physical examination comprises the fourth chapter, which brings out special details in examination. In this chapter the illustrations are profuse, well chosen and well done. The physiology of the female sex cycle, taken up in the fifth chapter, presents an extensive review of the literature, together with the author's own views. The illustrations here, several in color, together with numerous charts, make of the subject a reference work. In chapter six the cervical and vaginal secretions in relation to spermatozoa are discussed. In chapter seven, all methods of determining tubal patency and tubal occlusion are discussed and illustrated. The contention is made that regardless of all the fallacies and objections to tubal insufflation and hysterosalpingography, there is no doubt concerning the efficacy of both procedures from the diagnostic and therapeutic standpoints in sterility and fertility. In chapter eight treatment is elaborated. It deals with the endocrine factor, genital hygiene, control of venereal disease, premarital advice and examination, medical advice on fertility control, general treatment and specific treatment. The ninth chapter presents a rather complete review of the treatment of ovarian imbalance — endocrine, irradiation and surgery. The treatment of faulty reception of the spermatozoa, in its many modalities, is reviewed in the tenth chapter, and artificial insemination is discussed. The author's views on the subject are sound and conservative, he being of the opinion that only a small percentage of the patients who apply qualify for so radical a procedure. The concluding chapter deals with abortion in all its phases.

This well illustrated book presents an extensive bibliography, which in itself is a valuable contribution to the subject. It should serve not only as a textbook to the student of fertility but also as an important work of reference.

NOTICES

ANNOUNCEMENT

Dr. Joseph Igersheimer announces the removal of his office from 636 Beacon Street to 483 Beacon Street, Boston.

MEDICOLEGAL CONFERENCE AND SEMINAR

During the first week in October the departments of legal medicine of the medical schools of Harvard, Tufts and Boston University, in association with the Massachusetts Medico-Legal Society, will present a six-day program of lectures, conferences and demonstrations having to do with the investigation of deaths in the interests of public safety. Attendance during five of the six days of the course will be limited to fifteen persons who have registered in advance. On one day (October 3) the program will be open to any physician, lawyer, police official or senior medical student who may care to attend. Further information may be obtained from the secretary of the Massachusetts Medico-Legal Society, 25 Shattuck Street, Boston 15.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JULY 5

FRIDAY, JULY 6
*9:00–10:00 a.m. Medical clinic. Isolation Amphitheater, Children's Hospital.
10:50 a.m. Postgraduate clinic in dermatology and syphilology. Amphitheater, Mallory Building. Boston City Hospital.

MONDAY, JULY 9
*12:00 m.–1:00 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

TUESDAY, JULY 10
*9:00–10:00 a.m. Medical clinic. Infants' Hospital.
*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

WEDNESDAY, JULY 11
*12:00 m. Clinicopathological conference. Children's Hospital.

*Open to the medical profession.

SEPTEMBER 17. American Public Health Association. Page 752, issue of November 30.
OCTOBER 1–6. Medicolegal Conference and Seminar. Notice elsewhere on this page.